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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00 — A2

(11) International Publication Number: WO 00/54756

(43) International Publication Date: 21 September 2000 (21.09.00)

(21) International Application Number: PCT/CA00/00280

(22) International Filing Date: 15 March 2000 (15.03.00)

(30) Priority Data:
09/267,379 15 March 1999 (15.03.99) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS

(57) Abstract

Compounds and methods for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject are described. Neurological or cognitive conditions are treated by administering to a subject an effective amount of a therapeutic compound comprising a nitrate ester, or a pharmaceutically acceptable salt or ester thereof.

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NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS

FIELD OF THE INVENTION

This invention relates to nitrate esters and use thereof in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. More particularly, this invention relates to organic nitrates having therapeutic utility as neuroprotective agents and/or cognition enhancers. The invention still more particularly relates to nitrate esters bearing a sulfur or phosphorus atom β or γ to a nitrate group and their congeners which have therapeutic utility as neuroprotective agents and/or cognition enhancers.

BACKGROUND OF INVENTION

The nitrate ester glyceryl trinitrate (GTN) or nitroglycerin, has been used as a vasodilator in the treatment of angina pectoris for over a hundred years, and the dominant contemporary belief is that GTN exerts its therapeutic effect through *in vivo* release of nitric oxide (NO). Other organic nitrates, such as isosorbide dinitrate, have also been identified as effective and clinically important vasodilators. NO itself has been identified as Endothelium Derived Relaxing Factor (EDRF) and several classes of compounds, for example nitrosothiols, in addition to organic nitrates, have been proposed as NO donors or NO prodrugs. Well-known examples of these classes of compound and one nitrate, GTN itself, have been suggested to demonstrate neurotoxic or neuroprotective effects by dint of interactions with the redox modulatory site of the *N*-methyl-D-aspartate (NMDA) excitatory amino acid receptor. Thus GTN is firstly a potent vasodilator and secondly possesses

potential neuroprotective properties. Several attempts have been made to increase the efficacy or potency of alternative organic nitrates as vasodilators relative to GTN, for example, by incorporation of propanolamine or cysteine functionalities. However, no attempt has been made to separately regulate the vasodilatory and neuroprotective effects of GTN. Indeed, postural hypotension, weakness and other signs of cerebral ischemia are adverse effects, associated with the vasodilatory effects of GTN and observed in treatment, which are highly contraindicative of GTN itself, and by extrapolation GTN derivatives (1,2,3-trinitratopropane derivatives), as clinically useful neuroprotective therapeutic agents.

OBJECTS AND SUMMARY OF THE INVENTION

In as much as the potent vasodilatory effects of organic nitrates may prove (a) deleterious to, or alternatively (b) synergistic with the neuroprotective effects of GTN, it is postulated herein that regulation of these two effects is required for development of new and useful neuroprotective therapeutic agents. Further, it is postulated that such regulation may be achieved through use of an appropriate organic nitrate, such as, for example, nitrate esters incorporating sulfur-containing or phosphorus-containing functionalities into the structure of the nitrate esters or through use of their congeners. Interaction of organic nitrates with amino acid neurotransmitter receptors, including the NMDA receptor, will provide examples of compounds with neuroprotective properties, but modulation of the γ-aminobutyric acid type A ($GABA_A$) receptor response will provide examples of organic nitrates capable of cognition enhancement. Stimulation of cerebral soluble guanylyl cyclase (GCase) by organic nitrates, in particular selectively over arterial GCase, will provide examples of compounds with neuroprotective properties. Organic nitrates bearing antioxidant functionalities and those capable of inhibiting apoptosis will also provide examples of compounds with neuroprotective properties. These postulates are based, in part, on bioassay data on such compounds. Thus, there is a need for synthetic organic nitrates, such as, for example, nitrate esters containing sulfur or phosphorus functionalities or their congeners, as new and useful therapeutic agents for use in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. It will be appreciated, therefore, that these compounds can be used for

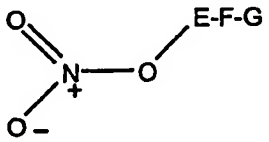
treatment conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amylotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; dementias of all type, trauma, drug-induced brain damage, aging.

It is an object of the present invention to provide novel organic nitrates, including aliphatic nitrate esters bearing a sulfur or phosphorus moiety β or γ to a nitrate group, or congeners thereof. Another object of the present invention is to provide methods for making such novel organic nitrates. Another object of the invention is to provide methods for effecting neuroprotection, mitigating neurodegeneration and /or effecting cognition enhancement employing organic nitrates. Another object of the present invention is to provide novel drugs as neuroprotective agents. Yet another object of the present invention is to provide novel drugs for use in cognition enhancement.

This invention provides novel compounds, methods and pharmaceutical compositions which are useful in the treatment of neurological disorders requiring mitigation of neurodegeneration, neuroprotection and/or cognition enhancement. Methods of the invention involve administering to a subject in need thereof a therapeutic compound which provides neuroprotection or cognition enhancement. Accordingly, the compositions and methods of the invention are useful for effecting neuroprotection or cognition enhancement in disorders in which neurotoxic damage occurs. The methods of the invention can be used therapeutically to treat conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amylotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage;

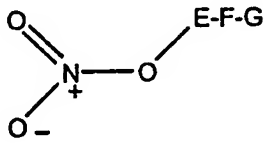
environmental excitotoxins; dementias of all type, trauma, drug-induced brain damage, and aging or can be used prophylactically in a subject susceptible or predisposed to these conditions. In certain embodiments, a therapeutic compound used in the method of the invention preferably can interact with GCase effecting neuroprotection and/or cognition enhancement. In other embodiments, a therapeutic compound used in the method of the invention preferably can modulate glutamate and/or non-glutamate neuroreceptor interactions effecting neuroprotection and/or cognition enhancement.

The invention relates to organic nitrates, i.e., nitrate esters. In one aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions, such that neurodegeneration is mitigated in the subject.

In another aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the

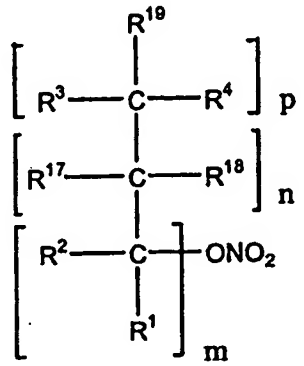


formula (Formula I):

wherein E, F, G are organic radicals which may contain inorganic counterions, such that cognition enhancement is effected.

In a further aspect, the invention provides use of therapeutic compounds that mitigate neurodegeneration, effect neuroprotection and/or effect cognition enhancement in a subject to

which the therapeutic compound is administered, the compounds having the formula (Formula II):



in which: m and n and p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, or amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino,

dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives, or are each independently hydrogen, a nitrate group, or W;

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that, when m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3 are nitrate groups; that R^4 is not H or C_1 – C_3 alkyl.

Preferred therapeutic compounds for use in the invention include compounds in which R^{19} is X-Y. In some preferred embodiments: R^{19} is X-Y and R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 or C_2 connections to R^1 – R^3 in cyclic derivatives; R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains, which may inlude one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which

rings optionally bear hydroxyl substituents; R^2 and R^4 are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R^5); and R^7, R^{11} are the same or different C_1 – C_8, alkyl or acyl.

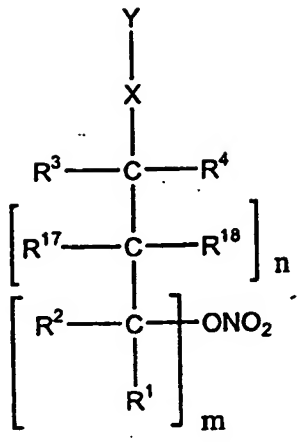
In certain embodiments in which R^{19} is X-Y, m, p = 1, and n = 0.

In other embodiments in which R^{19} is X-Y, X is selected from: CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, and SSR^4.

In other embodiments in which R^{19} is X-Y, Y is selected from CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist.

In certain embodiments, X and/or Y contain a sulfur-containing functional group. In some embodiments, a compound of the invention according to Formula II comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In further embodiments, a compound of the invention comprises a carbocyclic functionality, more preferably, a steroidal or carbohydrate moiety.

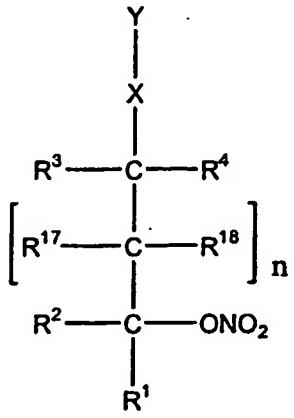
In another aspect, a therapeutic compound which is employed in methods of the invention is represented by the formula (Formula III):



in which: m is 1-10; R^{1-18} , X, and Y have the meaning as defined above. In some embodiments, R^6 - R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives. In certain preferred embodiments, R^{18} is A and n = 1.

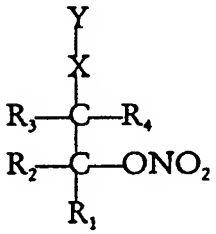
In another aspect, the invention provides novel compounds useful for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement which are represented by the structures of Formula 3.

In a further aspect, a therapeutic compound according to the invention is represented by the formula (Formula IV):



in which: R^3, R^1 = H; n, R^2R^{4-18}, X, and Y have the meaning as defined above. In certain preferred embodiments, X is CH_2 or does not exist, and Y is selected from: F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR_6, NR_6R_7, CN, NHOH, N_2H_3, $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3, S, SCN, $SCN_2H_2(R_{15})_2$, $SCN_2H_3(R_{15})$, $SC(O)N(R_{15})_2$, $SC(O)NHR_{15}$, SO_3M, SH, SR_7, SO_2M, $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_2HM, PO_3M_2, $P(O)(OR_{15})(OR_{16})$, $P(O)(OR_{16})(OM)$, $P(O)(R_{15})(OR_8)$, $P(O)(OM)R_{15}$, CO_2M, CO_2H, CO_2R_{11}, $C(O)R_{12}$, $C(O)(OR_{13})$, $C(O)(SR_{13})$, SR_5, SSR_7 and SSR_5. In certain embodiments, R_2 and R_4 are optionally H, a nitrate group or a connection to R_5-R_{16} in cyclic derivatives.

By one particular aspect of this invention there is provided an aliphatic nitrate ester containing at least one nitrate group, in which a S or P atom is situated β or γ to a nitrate group, or congeners thereof, having the general formula (Formula IV*):



where X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3, S, SCN, $SCN_2H_2(R_5)_2$, $SCN_2H_3(R_5)$, $SC(O)N(R_5)_2$, $SC(O)NHR_5$, SO_3M, SH, SR_7, SO_2M, $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_3M_2, $P(O)(OR_5)(OR_6)$, $P(O)(OR_6)(OM)$, $P(O)(R_5)(OR_8)$,

$P(O)(OM)R_5$, CO_2M, CO_2H, CO_2R_{11}, C(O), $C(O)R_{12}$, $C(O)(OR_{13})$, PO_2M, $P(O)(OR_{14})$, $P(O)(R_{13})$, SO, SO_2, $C(O)(SR_{13})$, SR_4, or SSR_4;

Y is SCN, $SCN_2H_2(R_5)_2$, $SC(O)NHR_5$, $SC(O)N(R_5)_2$, SR_4, SR_{10}, SSR_{10}, SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR_5)(OR_6)$, or $P(O)(OR_6)(OM)$, CN, N_3, $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, CO_2M, CO_2H, CO_2R_{11}, $C(O)R_{12}$, $C(O)(SR_{13})$, or does not exist;

R_5, R_6, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, are the same or different alkyls containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents or C_1 or C_2 connections to R_1 - R_3 in cyclic derivatives;

R_7, R_{11} are C_1 - C_8, alkyl or acyl;

R_2 and R_4 are the same or different and selected from H, ONO_2, C_1-C_4 alkyl optionally bearing 1-3 nitrate groups, and acyl groups (-$C(O)R_{10}$);

R_1 and R_3 are the same or different and selected from H, C_1-C_4 alkyl and chains, which may rings optionally bear hydroxyl substituents; and

M is H, Na^+, K include one O, linking R_1 and R_3 to form pentosyl, hexosyl, cyclopentyl or cycohexyl rings, which $^+$, NH_4^+ or $N^+H_nR_{11(4-n)}$ where n is 0-3;

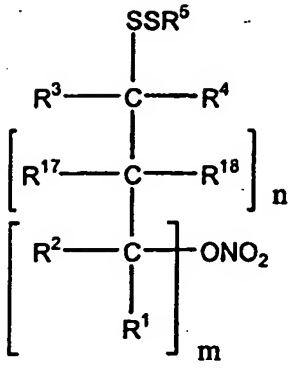
with the proviso that, when X is O, Y is not COR_{12}; and

with the proviso that, when R_3 is H, R_6 is not ethyl or n-butyl;

and pharmaceutically acceptable salts thereof.

The invention further provides a pharmaceutical composition comprising an effective amount of nitrate ester of Formula IV*, in admixture with a physiologically acceptable carrier therefor. The invention still further provides a method for effecting neuroprotection in a subject in need thereof comprising administering to said subject an effective amount of a nitrate ester of Formula IV*.

In yet another aspect of the invention, compounds according to the invention are represented by the formula (Formula V):



where m, n, R^{1-18} , X, and Y have the meaning as defined above.

In another aspect, the invention provides methods for preparing organic nitrates represented by the structures of Formula V.

The therapeutic compounds of the invention are administered to a subject by a route which is effective for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement. Suitable routes of administration include sublingual, oral, buccal, transdermal, nasal, subcutaneous, intravenous, intramuscular and intraperitoneal injection. Preferred routes of administration are intravenous, subcutaneous and transdermal administration, particularly for effecting neuroprotection. In addition, for effecting cognition enhancement, oral administration may be preferred. The therapeutic compounds can be administered with a pharmaceutically acceptable vehicle.

The invention also provides methods for treating a disease state associated with neurodegeneration by administering to a subject an effective amount of a therapeutic compound having a formula as set forth above, such that a disease state associated with neurodegeneration is treated.

The invention provides methods for effecting neuroprotection and/or cognition enhancement by administering to a subject an effective amount of a therapeutic compound

having a formula described above, such that neuroprotection and/or cognition enhancement is effected.

The invention further provides pharmaceutical compositions for treating neurodegeneration. The pharmaceutical compositions include a therapeutic compound of the invention in an amount effective to mitigate neurodegeneration in admixture with a pharmaceutically acceptable carrier therefor.

The invention also provides packaged pharmaceutical compositions for treating neurodegeneration. The packaged pharmaceutical compositions include a therapeutic compound of the invention and instructions for using the pharmaceutical composition for treatment of neurodegeneration.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a graph showing the effect of GTN with added L-cysteine (2mM) on soluble guanylyl cyclase (GCase) activity in rat aorta homogenate. Bars represent the mean ± standard errors calculated separately for each point.

Figure 2 is a graph showing the effect of IVd neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate normalized to the maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 3 is a graph showing the effect of IVg neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to the maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 4 is a graph showing the effect of IVb neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 5 is a graph showing the effect of IVf neat (diamonds); with added L-cysteine (2mM, triangles; 5mM circles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 6 is a graph showing the effect of IVe neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 7 is a graph showing the effect of IVj neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 8 is a graph showing the effect of IVa neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean ± standard errors calculated separately for each point.

Figure 9 is a graph showing a comparison of GTN (squares), IIIm (circles) and IVh (triangles) with added L-cysteine (1 mM) on soluble GCase activity in rat aorta homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean of duplicate determinations carried out in identical GCase preparations.

Figure 10 is a graph showing a comparison of GTN (squares), Va (circles) and Vb (triangles) with added L-cysteine(1 mM) on soluble GCase activity in rat aorta homogenate homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean ± standard errors calculated separately for each point (n=8-11).

Figure 11 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), Va (stippled bar), or IIIm (hatched bar). Segments of rat aorta were exposed to diluent, 1 μM drug (a), or 10μM drug (b) for 1 min. and cyclic GMP content determined by radioimmunoassay. Data are the mean ± standard errors (a, n=8; b, n=5).

Figure 12 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), IVk (stippled bar),Vb (cross-hatched bar), or Vc (hatched bar). Segments of rat aorta were exposed to diluent, 1 μM drug (a), or 10μM drug (b) for 1 min and cyclic GMP content determined by radioimmunoassay. Data are the mean ± standard errors (a, n=5; b, n=4).

Figure 13 is a graph showing cyclic GMP accumulation in rat hippocampal slices induced by diluent (Basal, open bar), GTN (filled bar), and Va (stippled bar). Sections of rat hippocampus (400 μm) were prepared and exposed to diluent, 10 μM drug (a) or 100 μM drug (b) for 3 min and cyclic GMP content determined by radioimmunoassay. Data are the mean ± standard errors (a, n=4; b, n=5).

Figure 14 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), Va (open triangles), compound IVc (diamonds), compound IVd (open squares), compound IVf (triangles), and compound IVg (open diamonds). Data points represent the mean ± standard errors (n=5-8).

Figure 15 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), IVk (open triangles), Vb (diamonds), IIIm (open squares), Vc (triangles), and IVh (open diamonds). Data points represent the mean ± standard errors (n=3-8).

Figure 16 is a graph showing relaxation induced by t-Bu nitrosothiol in isolated rat aorta. Data points represent the mean ± standard deviation (n=3).

Figure 17 is a graph showing relaxation induced by compound Ivd (a) and IVc (b) in untreated (squares) and GTN-tolerant (triangles) isolated rat aorta. Aortae were made tolerant by treatment with 0.5 mM GTN for 30 min. Data points represent the mean ± standard deviation (n= 3-6).

Figure 18 is a graph showing a comparison of the percent change in mean arterial pressure in conscious unrestrained rats after subcutaneous administration of 400 µmol/kg GTN (squares) or Va (open circles). Data points represent the mean ± standard errors (n=6).

Figure 19 is a graph showing a comparison of the percent change in mean arterial pressure in Inactin anaesthetized rats after intravenous bolus injection of GTN (squares) or Va (open circles). Data points represent the mean ± standard errors (n=4).

Figure 20 is a graph showing plasma levels (µM) of Vb (circles) and its mononitrate metabolite Vc (open squares) after subcutaneous administration of 200 µmol/kg Vb in conscious unrestrained rats. Data points represent the mean of two experiments.

Figure 21 is a graph showing the effect of compound Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean ± standard errors (n=8). *, $P< 0.05$ compared to ischemia.

Figure 22 is a graph showing the effect of delayed administration of Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean ± standard errors (n=6). *, $P<0.05$ compared to ischemia.

Figure 23 is a graph showing the effect of blocking guanylyl cyclase with ODQ on the neuroprotective properties of Va in rat hippocampal slices subjected to a 30-min period of *in vitro* ischemia. Data are the mean ± standard errors (n=4).

Figure 24 is a graph showing viable neurons in the CA1 region of the gerbil hippocampus after global cerebral ischemia. Data are the mean ± standard error for the number of animals in parentheses. *, $P< 0.05$ compared to vehicle control.

Figure 25 is a graph showing the total and cerebral cortical infarct volume of rat brain after a 2-hour period of focal cerebral ischemia. Data are the mean ± standard errors (n=10).

Figure 26 is a graph showing the effect of GTN (0.2. or 0.4 mg/hr by subcutaneous patch) on NMDA-induced loss of striatal tyrosine hydroxylase (TH) activity in the rat.

Figure 27 is a graph showing the effect of GTN (0.4 mg/hr by subcutaneous patch) implanted one hour after an infusion of NMDA into the substantia nigra on striatal TH activity. ** $P < 0.05$ compared to animals receiving NMDA alone.

Figure 28 is a graph showing the percent decrease in striatal TH activity in rats pretreated with GTN compared to Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN. Animals pretreated with GTN showed significant amounts of neuroprotection; whereas, animals pretreated with Losartan did not show any evidence of neuroprotection.

Figure 29 is a graph showing the blood pressure profiles of animals administered (a) GTN (0.4 mg/hr by subcutaneous patch), or (b) losartan (30 mg/kg by intraperitoneal injection).

Figure 30 is a graph showing the effect of compound IVd (Bunte salt, 10-100 μM) on GABA receptor-activated membrane current recorded in an oocyte expressing the $\alpha 1\beta 2\gamma 2L$ isoform of the $GABA_A$ receptor.

Figure 31 is a graph showing that nitric oxide donors have no effect on $GABA_A$ receptors expressed in *Xenopus* oocytes.

Figure 32 is a graph showing that the concentration-response relationship for activation of the $GABA_A$ receptor is altered in a non-competitive manner by compound IVd (Bunte salt).

DETAILED DESCRIPTION OF INVENTION

This invention pertains to methods and compositions useful for treating neurodegeneration. The methods of the invention involve administering to a subject a therapeutic compound which effects neuroprotection and/or cognition enhancement. Neuroprotection and/or cognition enhancement can be effected, for example, by modulating an interaction with guanylyl cyclase (GCase), a glutamate or non-glutamate neuroreceptor or attenuating free radical damage. GCase is the enzyme responsible for cGMP production in various areas of the brain.

According to certain aspects of the invention, neurodegeneration is mitigated by stimulating cerebral GCase. One of the major targets for organic nitrates is GCase activation, resulting in the production of cGMP. Experimental evidence obtained in a number of *in vitro* model systems supports the notion that elevated levels of cGMP help to prevent apoptotic (programmed) cell death. Thus, a cGMP-dependent mechanism significantly increases the

survival of trophic factor-deprived PC12 cells and rat sympathetic neurons (Farinelli et al., 1996), and of primary cultures of rat embryonic motor neurons (Estevez et al., 1998). The mechanism of action for organic nitrates in preventing apoptotic cell death may be inhibition of caspase-3 activation indirectly through elevations in cGMP levels or directly via protein S-nitrosylation of the enzyme by an NO-intermediate (Kim et al., 1997). Caspase-3 is a member of the cysteine protease family of enzymes that are essential for the execution step in apoptosis (Cohen, 1997; Nicholson and Thornberry, 1997). Activation of caspase-3 is required for apoptotic cell death in trophic factor-deprived PC12 cells (Haviv et al., 1997) and in glutamate-mediated apoptotic cell death of cultured cerebellar granule neurons (Du et al., 1997). In animal models of cerebral ischemia, caspase-3 activity is induced and may be responsible for the apoptotic component of delayed neuronal cell death (Chen et al., 1998; Namura et al., 1998; Ni et al., 1998). Inhibitors of caspase-3 significantly decrease the apoptotic component of delayed neuronal cell death in response to ischemic injury both *in vitro* (Gottron et al., 1997) and *in vivo* (Endres et al., 1998). A secreted region of the Alzheimer's disease β-amyloid precursor protein lowers intracellular calcium levels and provides neuroprotective effects on target cells through increases in cGMP levels and activation of protein kinase G (Barger et al., 1995; Furukawa et al., 1996). In preferred embodiments of the methods of the invention, nitrated molecules that have the capacity to activate GCase directly or via release of an NO-containing intermediate are used to modulate GCase activity.

According to certain other aspects of the invention, cognition enhancement (e.g., improved memory performance) is achieved by stimulating cerebral GCase. Several lines of experimental evidence support the notion that GCase and cGMP are involved in the formation and retention of new information. cGMP has been directly implicated in both long-term potentiation (LTP) and long-term depression (LTD), which are proposed cellular models for learning and memory (Arancio et al., 1995; Wu et al., 1998). In animal models, elevation of hippocampal cGMP levels leading to increased protein kinase G activity has been shown to be important for retention and consolidation of new learning (Bernabeu et al., 1996, 1997). Thus, stimulation of cerebral GCase activity is expected to improve learning and

memory performance in individuals in whom cognitive abilities are impaired by injury, disease, or aging.

We have shown that novel organic nitrate esters have differential effects to activate soluble GCase and to cause cGMP accumulation in vascular and brain tissue. There is a clear dissociation between the vascular relaxation effects of organic nitrate esters and ability to effect neuroprotection. Activation of GCase and accumulation of cGMP have been shown to be important in the neuroprotection of hippocampal brain slices subjected to a period of *in vitro* ischemia.

Cerebral ischemia results in marked increases in the release of the excitatory amino acid glutamate in the affected brain region (Bullock et al., 1998; Huang et al., 1998; Yang et al., 1998). In both humans (Bullock et al., 1998) and experimental animals (Huang et al., 1998; Goda et al., 1998; Yang et al., 1998), the amount of glutamate released during ischemia is positively correlated with the extent of brain injury. In experimental animal models of cerebral ischemia, decreased release of glutamate during ischemia (Goda et al., 1998) or blockade of glutamate receptors with antagonists (Ibarrola et al., 1998; O'Neill et al., 1998; Umemura et al., 1997) significantly reduces the extent of brain injury. However, these interventions are only effective when given prior to or during the ischemic insult. To be broadly useful, a therapeutic intervention is preferably effective when administered after the period of ischemia. We have designed a class of novel organic nitrate esters having high efficacy in effecting neuroprotection *in vivo* in models of transient global and focal cerebral ischemia when given after the ischemic insult. It will be appreciated, therefore, that these organic nitrates can be used for treatment of conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amylotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular

hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; and the like.

The direct effects of organic nitrates on amino acid neurotransmitter receptors has been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp recording methods. Organic nitrates were found to have direct, modulatory effects on $GABA_A$ receptor function (see Working Examples below). These allosteric modulatory effects of organic nitrates were not shared by direct NO-generating compounds, indicating a novel mechanism of action for organic nitrates to interact with $GABA_A$ receptors. In behavioural models of learning and memory, drugs which decrease $GABA_A$ receptor function improve performance on learning and memory tasks (Venault et al., 1992). Thus, the behavioural effect of organic nitrates, developed to act as modulators of $GABA_A$ receptor function, will be to improve memory performance and cognition in patient populations. It will be appreciated, therefore, that these organic nitrates can be used for treatment of conditions including but not limited to: stroke; dementias of all type; trauma; drug-induced brain damage; and aging.

According to certain aspects of the invention, neurodegeneration is mitigated by inhibition of free radical damage. Reoxygenation and reperfusion after a period of ischemia contributes significantly to the development of brain injury. Oxygen radicals, especially superoxide and peroxynitrite, formed in the period after an ischemic event may initiate processes such as breakdown of membrane lipids (lipid peroxidation), leading to loss of cell membrane integrity and inhibition of mitochondrial function (Macdonald and Stoodley, 1998; Gaetani et al, 1998). Oxidative stress is also believed to be one factor involved in initiation of apoptotic neuronal cell death (Tagami et al., 1998). In experimental animal models of ischemic brain injury, free radical scavengers and enhanced activity of superoxide dismutase have been found to reduce the extent of neuronal injury and cell death (Chan et al., 1998; Mizuno et al., 1998; Tagami et al., 1998). In preferred embodiments of the methods of the invention, nitrated molecules which have the capacity to inhibit production of free radicals and/or which act as free radical scavengers are used to attenuate the brain injury that occurs

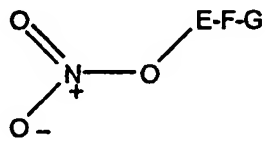
after a period of cerebral ischemia. It will be appreciated by those skilled in the art, that any organic nitrate in which vasodilatory potency is reduced and neuroprotective potency increased, represents a new and useful therapeutic agent for use in neuroprotection, particularly in treatment of conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amylotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin. GTN itself, proposed as a neuroprotective agent, has no clinical utility as a neuroprotective agent in therapy owing to its extraordinarily high vasodilatory potency. Similarly, by extrapolation, 1,2,3-trinitratopropane (GTN) derivatives are not expected to have clinical utility as neuroprotective agents in therapy owing to their especially high vasodilatory potency.

It will additionally be appreciated by those skilled in the art, that the use in therapy of any organic nitrate in cognition enhancment, represents a new and useful treatment for cognition enhancement, particularly in treatment of conditions including but not limited to: stroke; dementias of all type, trauma, drug-induced brain damage, and aging.

"Mitigating neurodegeneration" as use herein involves effecting neuroprotection, inhibiting or preventing neurodegeneration, and/or ameliorating the manifestations or impact of neurodegeneration. Such amelioration includes effecting cognition enhancement, as is quantified by tests known in the art (e.g., Venault et al., 1992, incorporated herein by reference). "Modulating" a biological process as used herein (for example, modulating the activity of the non-glutamate neuroreceptors), encompasses both increasing (positively moduclating) and decreasing (negatively modulating) such activity, and thus inhibition, potentiation, agonism, and antagonism of the biological process.

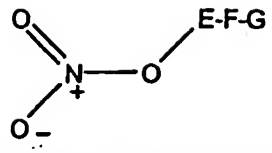
In particular, the therapeutic compounds of the invention comprise at least one nitrate group. The nitrate groups(s) can optionally be covalently bound to a carrier moiety or molecule (e.g., an aromatic group, an aliphatic group, peptide, steroid, nucleoside, peptidomimetic, steroidomimetic, or nucleoside analogue, or the like). In addition to functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to traverse biological membranes and to be biodistributed preferentially, without excessive or premature metabolism. Further, in addition to functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to exert amplified neuroprotective effects and/or cognition enhancement through synergism with the nitrate functionality.

In one aspect, the invention provides a method of treating a neurological condition and/or preventing an undesirable mental condition (e.g., memory loss) including the step of administering to a subject an effective amount of a therapeutic compound capable of mitigating neurodegeneration which has at least one nitrate group. In one embodiment, the therapeutic compound is capable of effecting neuroprotection. In another embodiment of the invention, the therapeutic compound is capable of effecting cognition enhancement. The therapeutic compound has the formula (Formula I):



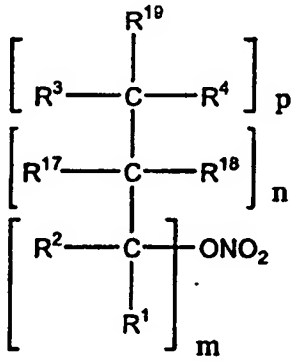
wherein E, F, G are organic radicals which may contain inorganic counterions; so that a neurological condition is treated.

In another aspect, the invention provides a pharmaceutical composition including a physiologically acceptable carrier and a compound having the formula (Formula I):



wherein: E, F, G are organic radicals which may contain inorganic counterions; such that neurodegeration is mitigated. The composition is employed for mitigating neurodegeneration, effecting neuroprotection and /or effecting cognition enhancement.

In another aspect, therapeutic compounds of the invention that effect neuroprotection and/or effect cognition enhancement in a subject to which the therapeutic compound is administered have the formula (Formula II):



in which: m, n, p are integers from 0 to 10; $R^{3,17}$ are each independently hydrogen, a nitrate group, or A; $R^{1,4}$ are each independently hydrogen or A, where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5

carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g., C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy ; R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y; where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5; Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist; R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion.

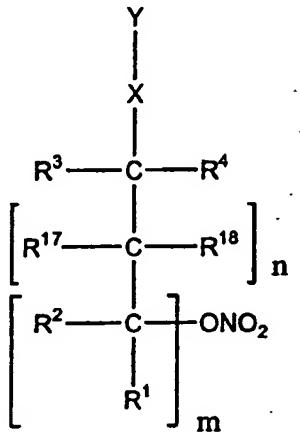
Pharmaceutical compostions comprising a compound of Formula II in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting europrotection and/or effecting cognition enhancement in a subject comprising the step of administering a

compound of Formula II to a subject such that said mitigation and /or said neuroprotection an/or cognition enhancement occurs.

According to this aspect of the invention, preferred therapeutic compounds for effecting neuroprotection and/or cognition enhancement in a subject to which the compound is administered include compounds in which R^{19} is X-Y. In some preferred embodiments: R^{19} is X-Y and R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains, which may inlude one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which rings optionally bear hydroxyl substituents; R^2 and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R^5); and R^7, R^{11} are the same or different $C_1 - C_8$, alkyl or acyl.

In certain embodiments in which R^{19} is X-Y, m, p = 1, and n = 0. In other embodiments in which R^{19} is X-Y, X is selected from: CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SSR^4. In certain other embodiments in which R^{19} is X-Y, Y is selected from CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist. In some embodiments, X and/or Y contains a sulfur-containing functional group. In certain embodiments, the compound of the invention comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In other embodiments, the compound of the invention comprises a carbocyclic functionality, more preferably, a steroidal or carbohydrate moiety.

In another aspect of the invention, a therapeutic compound of the invention is represented by the formula (Formula III):

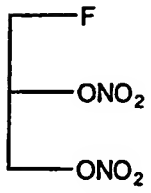


in which: m, n are 1-10; R^{1-18}, X, and Y have the meaning as defined above. In certain preferred embodiments, R^6 - R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives. In certain preferred embodiments, R^{18} is A and m = n = 1.

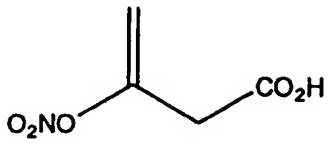
Pharmaceutical compostions comprising a compound of Formula III in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula III to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

Examples and preferred embodiments of compounds of the invention according to Formula III are set forth below:

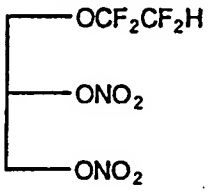
IIIa



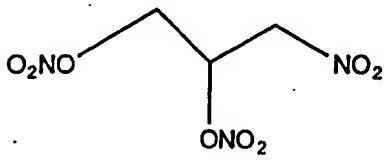
IIIb



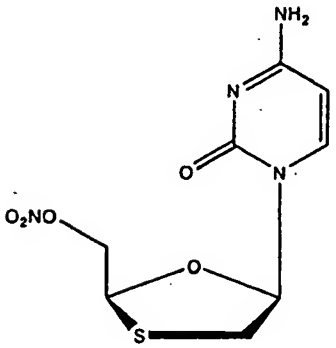
IIIc



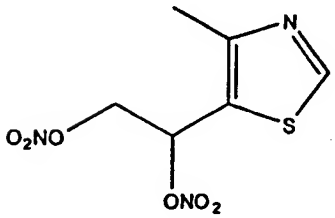
IIId



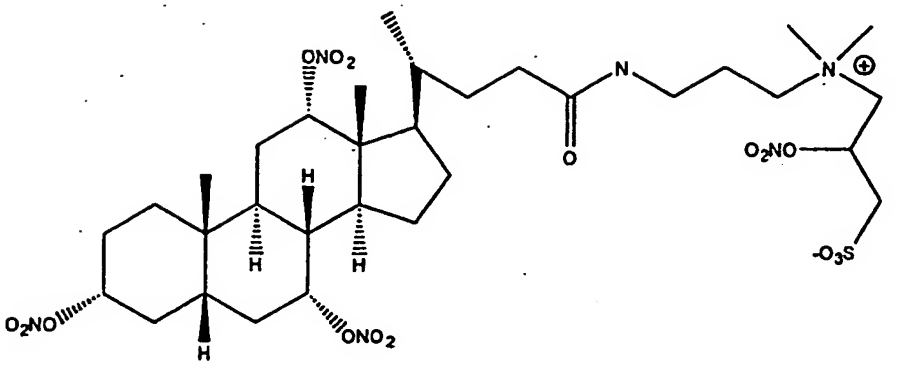
IIIe



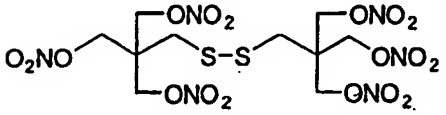
IIIf



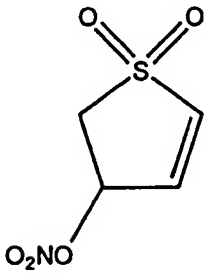
IIIg



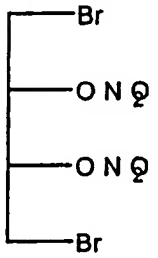
IIIh



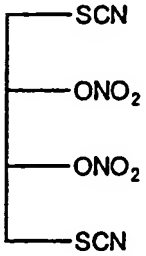
IIIi



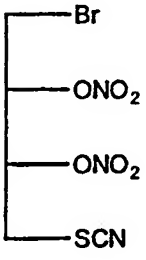
IIIj



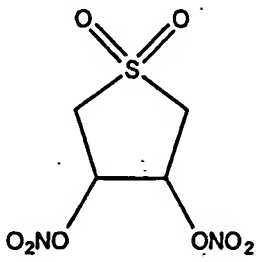
IIIk



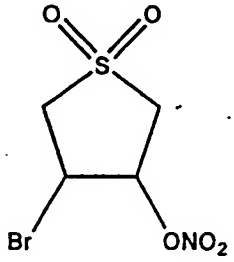
IIIl



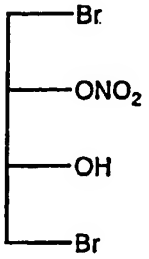
IIIm



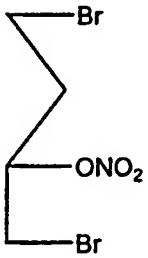
IIIn



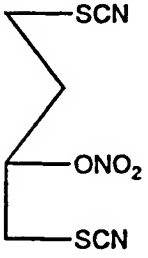
IIIo



IIIp

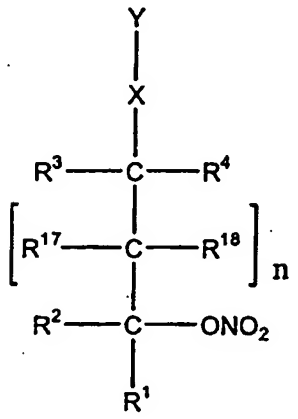


IIIq



IIIq

In another aspect of the invention, a therapeutic compound of the invention can be represented by the formula (Formula IV):

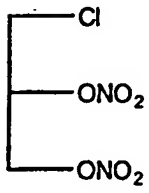


in which n = 0, X is CH_2 or does not exist, and Y is selected from F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR_6, NR_6R_7, CN, NHOH, N_2H_3, $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3, S, SCN, $SCN_2H_2(R_{15})_2$, $SCN_2H_3(R_{15})$, $SC(O)N(R_{15})_2$, $SC(O)NHR_{15}$, SO_3M, SH, SR_7, SO_2M, $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_2HM, PO_3M_2, $P(O)(OR_{15})(OR_{16})$, $P(O)(OR_{16})(OM)$, $P(O)(R_{15})(OR_8)$, $P(O)(OM)R_{15}$, CO_2M, CO_2H, CO_2R_{11}, $C(O)R_{12}$, $C(O)(OR_{13})$, $C(O)(SR_{13})$, SR_5, SSR_7 or SSR_5. R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, and R_{16} are as defined above. In certain preferred embodiments, R_2 and R_4 are optionally H, a nitrate group or a connection to R_5-R_{16} in cyclic derivatives.

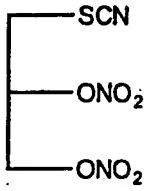
Pharmaceutical compostions comprising a compound of Formula IV in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula IV to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

Examples and preferred embodiments of compounds of the invention according to Formula IV are set forth below:

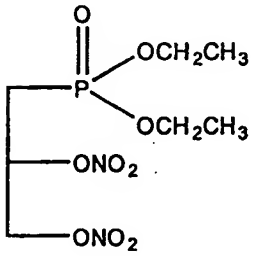
IVa 3



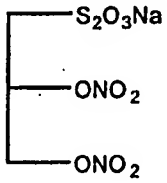
IVb 5



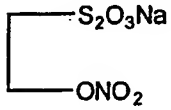
IVc 8



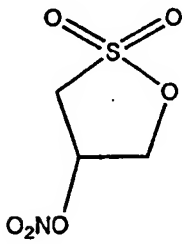
IVd 9



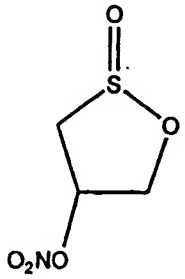
IVe 10



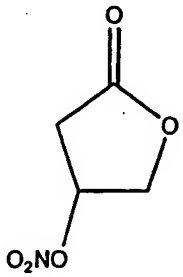
IVf 16



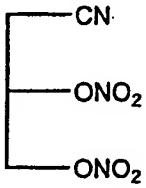
IVg 17



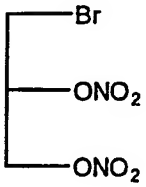
IVh 18



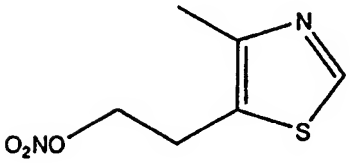
IVi



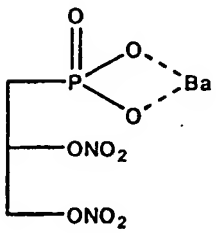
IVj



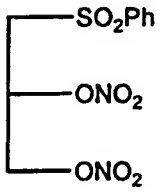
IVk 61



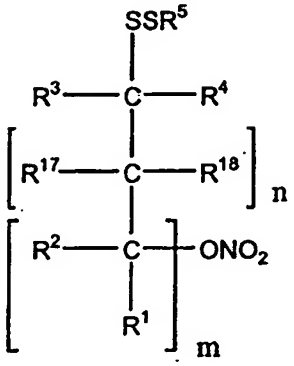
IVl



IVm



In yet another aspect of the invention, a compound of the invention can be represented by the formula (Formula V):

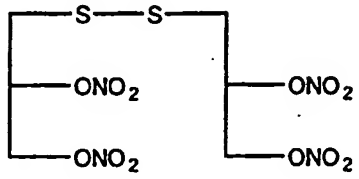


in which R_2 is optionally H or a connection to R_5 in cyclic derivatives, R_4 is H or a nitrate group, and R_5 is as described above.

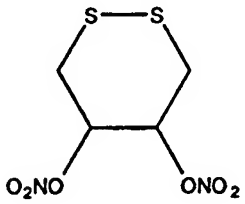
Pharmaceutical compostions comprising a compound of Formula V in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula V to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

Examples and preferred embodiments of compounds of the invention according to formula V (Formulae Va-c) are set forth below:

Va 15



Vb 33



Vc 50

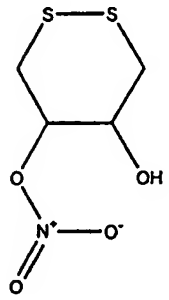


Table 1 lists data determined for compounds of the invention per art-recognized characterization techniques.

Table 1	^{1}H NMR	^{13}C NMR
IIIa	($CDCl_3$): 5.34-5.57 (1H, dm, $^3J_{HF}$ 20.6), 4.53-4.87 (4H, superposition several multiplets, O_2NO-$C\underline{H}_2$ + $C\underline{H}_2F$, $^2J_{HF}$ 46.7, $^4J_{HF}$ 0.66)	($CDCl_3$): 79.47 (d, $^1J_{CF}$ 177), 76.73 (d, $^2J_{CF}$ 20.6), 67.84 (d, $^3J_{CF}$ 6.87)
IIIb	($CDCl_3$): δ	($CDCl_3$): δ
IIIc	($CDCl_3$): δ 5.7 (1H, t, $^2J_{HF}$ 54), 5.45 (1H, m), 4.5-4.9 (2H, m), 4.15-4.35 (1H, m)	($CDCl_3$): δ 75.55, 68.05, 60.76
IIId	($CDCl_3$): δ 5.46 (1H, m), 4.80-4.87 (1H, dd, J 3.5, 12.9), 4.65-4.72 (1H, dd, J 6.2, 12.9), 3.7-3.8 (2H, m)	($CDCl_3$): δ 77.24, 68.57, 39.86
IIIf	($CDCl_3$) δ 8.72 (s, 1H), 5.38 (t, 1H), 4.6 (d, 2H), 2.45 (s, 3H)	-
IIIg	($DMSOd_6$) $C\underline{H}ONO_2$ only: δ 4.8-5.8	($DMSOd_6$) $\underline{C}ONO_2$ only: δ 85.68, 84.17, 82.47, 76.50

IIIh	(CD_3OD) δ 4.85 (3H, m), 3.5 (1H, m)	(CD_3OD) δ 70.61, 36.74
IIIi	($CDCl_3$): δ 6.95 (dd, 1H), 6.71 (dd, 1H), 6.09 (m, 1H), 3.80 (dd, 1H), 3.32 (dd, 1H)	($CDCl_3$): δ 137.9, 132.5, 76.6, 52.9
IIIj	($CDCl_3$): δ 5.62 (2H, m), 3.60 (4H, m)	($CDCl_3$): δ 77.87, 25.22
IIIk	(CD_3CN): δ 3.45 (m, 2H), 5.72 (m, 2H)	(CD_3CN): δ 79.98, 28.87
IIIl	-	(CD_3CN): δ 79.48, 33.45, 28.47
IIIm	($DMSOd_6$): δ 5.97 (m, 2H), 3.80 (m, 4H)	($DMSOd_6$): δ 78.84, 52.60
IIIn	($CDCl_3$): δ 5.73 (m, 1H), 4.62 (m, 1H), 3.96-3.77 (m, 1H), 3.58-3.32 (m, 1H)	($CDCl_3$): δ 81.47, 57.85, 53.50, 38.75
IIIo	-	($CDCl_3$): δ 81.24, 69.79, 33.26, 27.24
IIIp	($CDCl_3$): δ 5.36 (m, 1H), 3.11-3.60 (m, 4H), 2.33 (m, 2H)	($CDCl_3$): δ 78.92, 33.66, 30.64, 27.36
IIIq	($CDCl_3$): δ 5.47 (m, 1H), 3.53-3.05 (m, 4H), 2.29 (m, 2H)	($CDCl_3$): δ 81.32, 37.12, 32.97, 30.98
IVi	($CDCl_3$): δ 5.45 (1H, m), 4.83 (1H, dd), 4.65 (1H, dd), 2.9 (2H, m)	(CD_3OD): δ 116.44, 75.37, 71.20, 19.19
IVk	($CDCl_3$) δ 8.55 (s, 1H), 4.55 (t, 2H), 3.15 (t, 2H), 2.37 (s, 3H)	($CDCl_3$) δ 150.9, 150.7, 125.3, 72.53, 24.47, 15.18
IVm	($CDCl_3$): δ 7.5-8.0 (arom, 5H), 5.7 (1H, m), 4.94 (1H, dd), 4.62 (1H, dd), 3.5 (2H, m)	($CDCl_3$): δ 135.45, 134.79, 129.81, 27.95, 73.08, 70.04, 54.73
Vb	($CDCl_3$) δ 5.56 (m, 2H), 3.38-2.95 (m, 4H)	(CD_3OD) δ 85.93, 32.77
Vc	($CDCl_3$): δ 5.85-5.91 (1H, m), 4.50-4.58 (1H, m), 3.22-3.29 (1H, dd, J 5.47, 12.78), 2.97-3.05 (1H, dd, J 4.6, 11.88), 2.82-2.90 (1H, dd, J 2.87, 12.78), 2.74-2.83 (1H, dd, J 3.15, 11.9)	($CDCl_3$): δ 87.6, 74.96, 36.20, 31.54

Methods for preparing organic nitrates represented by the structures of Formula III are provided by the invention and taught herein, particularly in the Working Examples below.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers (e.g., enantiomers, diastereomers) arising from such asymmetry are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by asymmetric synthesis. For the purposes of this application, unless

expressly noted to the contrary, a compound shall be construed to include both the R and S stereoisomers at each stereogenic center.

In certain embodiments, a therapeutic compound of the invention comprises a cation (i.e., in certain embodiments, one of X or Y includes a cation, e.g., in the compound of formula IVd). If the cationic group is a proton, then the compound is considered an acid. If the proton is replaced by a metal ion or its equivalent, the compound is a salt. Pharmaceutically acceptable salts of the therapeutic compound are within the scope of the invention. For example, M can be a pharmaceutically acceptable alkali metal (e.g. Li, Na, K), ammonium, alkaline earth metal (e.g. Ca, Ba, Mg), higher valency cation, or polycationic counter ion (e.g., polyammonium cation) (see e.g., Berge et al., 1977). It will be appreciated that the stoichiometry of an anionic portion of the compound to a salt-forming cation will vary depending on the charge of the anionic portion of the compound and the charge of the counterion. Preferred pharmaceutically acceptable salts include a sodium, potassium, or calcium salt, but other salts are also contemplated within their pharmaceutically acceptable range.

The therapeutic compound of the invention can be administered in a pharmaceutically acceptable vehicle. As used herein "pharmaceutically acceptable vehicle" includes any and all solvents, excipients, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like which are compatible with the activity of the compound and are physiologically acceptable to the subject. An example of the pharmaceutically acceptible vehicle is buffered normal saline (0.15 M NaCl). The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compound, use thereof in the compositions suitable for pharmaceutical administration is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Carrier or substituent moieties useful in the present invention may also include moieties which allow the therapeutic compound to be selectively delivered to a target organ. For example, delivery of the therapeutic compound to the brain may be enhanced by a carrier moiety using either active or passive transport (a "targeting moiety"). Illustratively, the carrier molecule may be a redox moiety, as described in, for example, U.S. Patents 4,540,654 and 5,389,623, both to Bodor. These patents disclose drugs linked to dihydropyridine moieties which can enter the brain, where they are oxidized to a charged pyridinium species which is trapped in the brain. Thus drugs accumulate in the brain. Other carrier moieties include compounds, such as amino acids or thyroxine, which can be passively or actively transported *in vivo*. Such a carrier moiety can be metabolically removed *in vivo*, or can remain intact as part of an active compound. Structural mimics of amino acids (and other actively transported moieties) including peptidomimetics, are also useful in the invention. As used herein, the term "peptidomimetic" is intended to include peptide analogues which serve as appropriate substitutes for peptides in interactions with, for example, receptors and enzymes. The peptodomimetic must possess not only affinity, but also efficacy and substrate function. That is, a peptidomimetic exhibits functions of a peptide, without restriction of structure to amino acid constituents. Peptidomimetics, methods for their preparation and use are described in Morgan et al. (1989), the contents of which are incorporated herein by reference. Many targeting moieties are known, and include, for example, asialoglycoproteins (see e.g., Wu, U.S. Patent 5,166,320) and other ligands which are transported into cells via receptor-mediated endocytosis (see below for further examples of targeting moieties which may be covalently or non-covalently bound to a target molecule).

In the methods of the invention, neurodegeneration in a subject is mitigated, and/or neuroprotection and/or cognition enhancement is effected, by administering a therapeutic compound of the invention to the subject. The term "subject" is intended to include living organisms in which the particular neurological condition to be treated can occur. Examples of subjects include humans, apes, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. As would be apparent to a person of skill in the art, the animal

subjects employed in the working examples set forth below are reasonable models for human subjects with respect to the tissues and biochemical pathways in question, and consequently the methods, therapeutic compounds and pharmaceutical compositions directed to same. As evidenced by Mordenti (1986) and similar articles, dosage forms for animals such as, for example, rats can be and are widely used directly to establish dosage levels in therapeutic applications in higher mammals, including humans.

In particular, the biochemical cascade initiated by cerebral ischemia is generally accepted to be identical in mammalian species (Mattson and Scheff, 1994; Higashi et al., 1995). In light of this, pharmacological agents that are neuroprotective in animal models such as those described herein are believed to be predictive of clinical efficacy in humans, after appropriate adjustment of dosage. Specifically, there are comparable memory-deficit patterns between brain-damaged rats and humans, which indicates that the rat can serve as an excellent animal model to evaluate the efficacy of pharmacological treatments or brain damage upon memory (Kesner, 1990). The only approved drug for the clinical treatment of occlusive stroke in humans is tissue plasminogen activator, which is administered at a dose of 0.9 mg/kg by intravenous injection (Wittkowsky, 1998). This drug is also effective in protecting the rat brain subjected to cerebral ischemia by occlusion of the middle cerebral artery, when administered at a dose of 10 mg/kg intravenously (Jiang et al., 1998). Thus, the rat model of focal cerebral ischemia used in the development of the novel organic nitrate esters described herein has been shown to be shown to be predictive of clinical efficacy with at least one other class of pharmacological agents.

As would also be apparent to a person skilled in the art, the invention further encompasses methods of the invention employed *ex vivo* or *in vitro*. For example, the Working Examples describe studies utilizing tissue homogenates according to the invention. Furthermore, diagnostic tests or studies of efficacy of selected compounds may conveniently be performed ex vivo or in vitro, including in animal models. Such tests, studies and assays are within the scope of the invention.

Administration of the compositions of the present invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to mitigate neurodegeneration, and/or to effect neuroprotection and./or cognition enhancement in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the amount of neurodegeneration that has already occurred at the clinical site in the subject, the age, sex, and weight of the subject, and the ability of the therapeutic compound to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention (e.g., Va) is between 0.5 and 500 mg/kg of body weight per day. In an aqueous composition, preferred concentrations for the active compound (i.e., the therapeutic compound that can mitigate neurodegeneration and /or effect neuroprotection and /or cognition enhancement) are between 5 and 500 mM, more preferably between 10 and 100 mM, and still more preferably between 20 and 50 mM.

The therapeutic compounds of the invention can be effective when administered orally. Accordingly, a preferred route of administration is oral administration. Alternatively, the active compound may be administered by other suitable routes such as transdermal, subcutaneous, intraocular, intravenous, intramuscular or intraperitoneal administration, and the like (e.g., by injection). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action of acids, enzymes and other natural conditions which may inactivate the compound.

The compounds of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB, they

can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Patents 4,522.811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs ("targeting moieties"), thus providing targeted drug delivery (see, e.g., Ranade et al., 1989). Exemplary targeting moieties include folate and biotin (see, e.g., U.S. Patent 5,416,016 to Low et al.); mannosides (Umezawa et al., 1988); antibodies (Bloeman et al., 1995; Owais et al., 1995); and surfactant protein A receptor (Briscoe et al., 1995). In a preferred embodiment, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety.

Delivery and *in vivo* distribution can also be affected by alteration of an anionic group of compounds of the invention. For example, anionic groups such as phosphonate or carboxylate can be esterified to provide compounds with desirable pharmocokinetic, pharmacodynamic, biodistributive, or other properties. Exemplary compounds include IVl and pharmaceutically acceptable salts or esters thereof.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

The therapeutic compound may also be administered parenterally (e.g., intramuscularly, intravenously, intraperitoneally, intraspinally, or intracerebrally). Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders

for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants.

Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In some cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient (i.e., the therapeutic compound) optionally plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of neurological conditions in subjects.

Therapeutic compositions can be administered in time-release or depot form, to obtain sustained release of the therapeutic compounds over time. The therapeutic compounds of the invention can also be administered transdermally (e.g., by providing the therapeutic compound, with a suitable carrier, in patch form).

Active compounds are administered at a therapeutically effective dosage sufficient to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in a subject. A "therapeutically effective dosage" preferably mitigates neurodegeneration by about 20%, more preferably by about 40%, even more preferably by about 60%, and still more

preferably by about 80% relative to untreated subjects. The ability of a compound to mitigate neurodegeneration can be evaluated in model systems that may be predictive of efficacy in mitigating neurodegeneration in human diseases, such as animal model systems known in the art (including, e.g., the method of transient middle cerebral artery occlusion in the rat) or by *in vitro* methods, (including, e.g., the assays described herein).

It will be appreciated that the ability of a compound of the invention to mitigate neurodegeneration will, in certain embodiments, be evaluated by observation of one or more symptoms or signs associated with neurodegeneration *in vivo*. Thus, for example, the ability of a compound to mitigate neurodegeneration may be associated with an observable improvement in a clinical manifestation of the underlying neurodegeneration-related disease state or condition, or a slowing or delay in progression of symptoms of the condition. Thus, monitoring of clinical manifestations of disease can be useful in evaluating the neurodegeneration-mitigating efficacy of a compound of the invention.

The method of the invention is useful for treating neurodegeneration associated with any disease in which neurodegeneration occurs. Clinically, neurodegeneration can be associated with conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amylotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant; animal and marine origin; dementias of all type; trauma; drug-induced brain damage; and aging; or result from surgical procedures such as cardiac bypass.

Novel compounds according to the invention can be synthesized by methods set forth herein (see, e.g., Working Examples) or in our patents U.S. No. 5,807,847 and U.S. No. 5,883,122. Various compounds for use in the methods of the invention are commercially

available and/or can be synthesized by standard techniques. In general, nitrate esters can be prepared from the corresponding alcohol, oxirane or alkene by standard methods, that include: nitration of alcohols and oxiranes, mixed aqueous/organic solvents using mixtures of nitric and sulfuric acid and/or their salts, with temperature control (see Yang et al., 1996); nitration of alcohols and oxiranes in acetic anhydride using nitric acid or its salts with or without added acid catalyst, with temperature control (see, e.g., Louw et al., 1976); nitration of an alcohol with a nitronium salt, e.g. a tetrafluoroborate; nitration of an alkene with thallium nitrate in an appropriate solvent (see Ouellette et al., 1976).

The following Examples further illustrate the present invention and are not intended to be limiting in any respect. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

Working Examples

Example 1

Characterization of guanylyl cyclase activation

Activation of soluble guanylyl cyclase (GCase) by nitrates IIIm, IVa, IVb, IVd, IVe, IVf, IVg, IVj, Va, Vb, and GTN was assayed employing partially purified enzyme freshly prepared from the 105,000g supernatant fraction of rat aorta homogenates, using the radioimmunoassay method described by Bennett et al. (1992), the disclosure of which is incorporated herein by reference. Dose-response curves were obtained for GCase activation by nitrates IVa, IVb, IVd, IVe, IVf, IVg, IVj, and GTN in the presence and absence of cysteine and dithiothretol (DTT; both 2mM). In all cases, data were normalized to the maximal GTN response carried out in identical GCase preparations. Experimental incubations were performed at 37°C for 10 min. The data from these curves are summarized in Figures 1-8, which give: concentrations of nitrates required to give a response equivalent to the maximal response seen for GTN+cysteine; the maximal response measured for each nitrate, and; where applicable, potency. The GCase assay data show that IVd activates GCase, with a

submillimolar EC_{50} in the absence of any added thiol, in contrast to GTN which requires added cysteine (Figs 1,2). Compounds IVd and IVg also activate GCase in the presence of DTT in contrast to GTN (Figs 2,3). Activation of GCase by IVb was cysteine-dependent and the response was very low (EC_{50} > 1mM) (Fig. 4). Activation of GCase by compound IVf was cysteine-dependent and much greater than that achieved by GTN (Fig. 5). Activation of GCase by compound IVe was very low under all conditions tested (Fig. 6). Activation of GCase by compounds IVj and IVa was cysteine-dependent and approximately equivalent to GTN (Figs. 7,8). Relative to GTN itself, a wide range of potencies was observed for the nitrate esters of the invention. No activation of GCase by glycerol mononitrates was observed in this assay at the concentrations of nitrate employed.

To test for potential differences in GCase activation by nitrates, the effects of IIIm, IVh, Va, Vb, and GTN were assayed in brain and vascular tissue. IVh had no effect on GCase activity in either rat aorta or rat hippocampus (Fig. 9). IIIm had greater efficacy to stimulate GCase activity compared to GTN in both rat aorta and rat hippocampus (Fig. 9). Vb was found to be equivalent to GTN in efficacy and potency for activation of GCase in both rat aorta and rat hippocampus (Fig. 10). Va was found to have greater efficacy, but equal potency, to GTN in rat aorta (Fig. 10a). In contrast, Va had greater efficacy and greater potency to stimulate GCase in rat hippocampus (Fig. 10b). These data illustrate that nitrates have differential effects on GCase activation that are dependent on both structure of the compound and the tissue assayed for GCase activity, supporting the notion that neuroprotective and cardiovascular effects of nitrates are separable.

Example 2

Characterization of cyclic GMP accumulation

In order to extend the GCase data further, the effects of nitrates Va, IIIm, Vb, Vc, and IVk on cyclic GMP accumulation in intact isolated rat aorta were examined (Figs. 11,12). Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994) and Stewart et al. (1989), both incorporated herein by

reference. Tissues were contracted submaximally with phenylephrine (0.1μM) and exposed to various concentrations of drug for 1 min. Cyclic GMP accumulation was determined using the radioimmunoassay method described by Bennett et al. (1992). At concentrations of 1 μM and 10 μM, GTN and IVk significantly increased cGMP accumulation (Figs. 11, 12). At a concentration of 1 μM, Va, IIIm, Vb, and Vc did not significantly increase cyclic GMP accumulation (Figs. 11a, 12a). At a concentration of 10 μM, Va, Vb, and IVk significantly increased cyclic GMP accumulation, whereas IIIm and Vc did not (Figs. 11b, 12b).

Sections of rat hippocampus (400 μm) were prepared and incubated in oxygenated Krebs solution at 37°C. After a 60-min equilibration period, the brain slices were stimulated with different concentrations of Va or GTN for 3-min. Cyclic GMP accumulation was determined as described above for aortic strips. Figure 13 shows that Va causes a concentration-dependent increase in the tissue levels of cGMP in rat hippocampal brain slices *in vitro* and that, at high concentration (100 μM), Va is more effective than GTN in elevating cGMP levels in hippocampal brain slices *in vitro*. These data are in very good agreement with the differential effects of Va and GTN on hippocampal GCase activity shown in Figure 10b.

Example 3

Characterization of relaxation of isolated blood vessels

In order to extend the GCase data, the relaxing effects of nitrates IIIm, IVc, IVd, IVf, IVg, IVh, IVk, Va, Vb, and Vc on rat aortic tissue were examined. Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994), and Stewart et al. (1989). Tissues were contracted submaximally with phenylephrine (0.1μM) and exposed to various concentrations of nitrovasodilator to obtain concentration-response curves. In this intact tissue assay, all of the nitrates were observed to cause relaxation of the tissue with a maximal relaxant response equal to that obtained with GTN. However, the compounds differed in potency with EC_{50} (effective concentration for 50% of the subjects) values of 7.87 nM, 94.3 nM, 6.59 μM, 25.2 μM, 11.0 μM, and 0.203 μM, for GTN and compounds Va, IVd, IVg, IVf, and IVc, respectively (Fig. 14). In another series

of experiments, the EC_{50} values for relaxation were 0.61 nM, 3.19 nM, 8.40 nM, 0.153 μM, 0.437 μM and 6.89 μM for GTN, IVk, Vb, IIIm, Vc, and IVh, respectively (Fig. 15). The EC_{50} value for a nitrosothiol (*tert*-butyl nitrosothiol, Fig.16) was 11.2 μM. Compounds IVd and IVc were tested for their ability to cause vascular relaxation in tissues that had been made tolerant to the relaxant effect of GTN. GTN tolerance was induced by incubating tissues with high concentrations of GTN (0.5mM GTN for 30 min). Under these conditions, the maximal relaxant effects of IVd (Fig.17a) and IVc (Fig.17b) were not significantly different from their effects for untreated tissue. The EC_{50} for relaxation was increased approximately threefold, but the difference was not statistically significant.

Example 4

Characterization of blood pressure changes in the whole animal

To test for differential effects of nitrates on blood pressure responses, Va and GTN were injected into rats in which the abdominal aorta was cannulated for blood pressure recording. In the first experiment, Va and GTN were injected subcutaneously at a dose of 400 μmol/kg body weight into conscious, freely moving animals. GTN caused a small and transient decrease in blood pressure in these animals, whereas Va had no discernable effect on arterial blood pressure (Fig. 18). Va and GTN were subsequently tested in anesthetized rats in which the abdominal vena cava was also cannulated to allow for bolus intravenous injection of drugs. In this preparation, GTN caused a substantial and dose-dependent decrease in arterial blood pressure. In contrast, Va at equal doses had very modest effects on blood pressure at doses lower than 2 μmol/kg body weight (Fig. 19). These data are in very good agreement with the results obtained for these two agents using the isolated blood vessel preparation.

The plasma levels of nitrates Vb and Vc (the denitrated metabolite of Vb) were measured to gain insight into the handling of these molecules in the body. Cannulas were placed in the abdominal aorta for blood sampling. After a two-day recovery period, a single subcutaneous dose of Vb (200 μmol/kg) was administered and blood samples collected over a period of six hours. Samples were centrifuged, the plasma collected, and the concentrations of

Vb and Vc determined by gas-liquid chromatography by the method of McDonald and Bennett (1990). The data obtained for Vb and Vc indicate that nitrates achieve maximal plasma levels within 30 minutes after subcutaneous injection, and therafter decline at a steady rate (Fig. 20). These data suggest that nitrates have excellent bioavailability after subcutaneous injection.

Example 5

Characterization of neuroprotection in brain slices

In order to test for potential neuroprotective properties, the effects of Va were tested in an *in vitro* model of cerebral ischemia. Rat hippocampal slices were subjected to 30 minutes of ischemia by incubation in a buffered salt solution lacking glucose and oxygen. Sections of rat hippocampus (400 μm) were prepared and incubated in oxygenated Krebs solution at 37°C. Slices were then either untreated or subjected to a 30-minute period of ischemia by incubation in Krebs solution lacking oxygen and glucose. Slices were then incubated for a further 4 hours in oxygenated Krebs solution in the presence of drug vehicle or 200 μM Va. At the end of the 4-hr re-oxygenation period, release of the cytosolic enzyme lactate dehydrogenase (LDH) from the tissue was used an index of neuronal cell injury. Some hippocampal slices were treated with Va (200 μM) after the 30-minute period of ischemia. Figure 21 shows that Va significantly reduced the release of LDH from ischemic brain slices when administered immediately after the period of ischemia. Figure 22 shows that Va was still effective at protecting ischemic brain slices *in vitro* when drug exposure was delayed for up to 1 hour after re-oxygenation of the tissue.

To test the mechanism of this neuroprotection, rat hippocampal brain slices made ischemic for 30 minutes *in vitro* were exposed to the guanylyl cyclase inhibitor ODQ 5-min prior to administration of 200 μM Va. The concentration of ODQ used was known to completely block the production of cGMP induced by Va. Blockade of guanylyl cyclase by ODQ completely eliminated the neuroprotective effect of Va in ischemic rat hippocampal

slices, showing that elevations in cGMP levels are directly related to the neuroprotective properties of Va *in vitro* (Fig. 23).

Example 6

Characterization of neuroprotection in the whole animal

To test the efficacy of nitrates in animal models of cerebral ischemia, two different approaches were taken. In the first, Mongolian gerbils were subjected to 5 minutes of global forebrain ischemia by occlusion of the common carotid arteries under halothane anesthesia. This period of ischemia produces a selective neuronal cell death in the CA1 region of the hippocampus that develops over several days. Surgical procedures, and control of brain and body temperature during the occlusion, were as described in Nurse and Corbett (1996), incorpated herein by reference. Animals were given two subcutaneous injections of drug vehicle, or 400 μmol/kg IVh, Vb or Va at 5-min and 90-min after the occlusion. Sham-treated animals had the carotid arteries exposed but not occluded. Seven days later, the brains were fixed by transcardiac perfusion with 4% paraformaldehyde, dissected out, embedded in paraffin, and 5 μm sections were cut and stained with cresyl violet. Viable neurons in 100 square μm blocks of the CA1 region were counted to obtain an index of neuronal cell damage. The results obtained with nitrates IVh, Vb, and Va are shown in Figure 24. Both Va and Vb produced a statistically significant neuroprotection against 5 minutes of global forebrain ischemia in the gerbil.

The second animal model tested was transient focal cerebral ischemia in the rat induced by occlusion of the middle cerebral artery. Under halothane anesthesia, a filament was advanced into the right internal carotid artery until the origin of the right middle cerebral artery was occluded. The filament was secured, the animal allowed to regain consciousness, and two hours later the filament was removed under halothane anesthesia. Animals were given five subcutaneous doses of drug vehicle or 200 μmol/kg Va at 2, 3, 4, 6, and 8 hr post-occlusion. At 24 hr post-occlusion the animals were sacrificed, the brain removed, cut into 2-mm coronal sections and stained for viable tissue with 2,3,5-triphenyltetrazolium. Infarct

volume of whole brain and cerebral cortex was quantitated by computer-assisted image analysis. A 2-hour episode of cerebral ischemia followed by recirculation produces a large infarct in the cerebral cortex and subcortical structures on the affected side. The volumes of the total and cerebral cortical infarct in the rat brain were very similar to those reported by other groups using the same procedure (e.g., Sydserff et al., 1995; Morikawa et al., 1998). Figure 25 shows the results obtained with nitrate Va in this model. A series of subcutaneous injections of Va at a dose of 200 μmol/kg body weight at 2, 3, 4, 6, and 8 hours after the onset of cerebral ischemia resulted in a statistically significant neuroprotection when assayed 24 hours after ischemia. Collectively, these data indicate that delayed administration of Va is neuroprotective in two different animal models of cerebral ischemia.

In a separate series of experiments, the effects of organic nitrates on focal excitotoxic lesions induced by localized application of NMDA in the rat brain were determined. Male Sprague-Dawley rats were stereotactically infused with NMDA into the right substantia nigra as described in Connop et al. (1995), incorporated herein by reference. Four days later, both striata were dissected and assayed for tyrosine hydroxylase (TH) activity. Loss of TH activity in the striata is a quantitative index of NMDA-induced neuronal cell death in the substantia nigra. The striata of each animal were compared to express neurotoxicity as a percent decrease in TH activity of the ipsilateral striatum as compared to the contralateral striatum. Pretreatment of these animals with GTN (administered as a subcutaneous patch inserted under halothane anesthesia one hour prior to the NMDA infusion) at doses of 0.2 and 0.4 mg/hr produced a dose-dependent reduction in the loss of TH activity from the ipsilateral striatum (Fig. 26). Figure 27 shows that delaying the administration of GTN until one hour after the NMDA infusion was equally effective at preventing NMDA-induced neuronal cell death in the substantia nigra. Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN, had no neuroprotective effects (Fig. 28). This shows that any vasorelaxation caused by GTN is not the mechanism of the neuroprotection against excitotoxic cell death induced by NMDA. Figure 29 shows that the doses of losartan and GTN used in these studies caused an equivalent decrease in systemic blood pressure. Male

Sprague-Dawley rats with aortic catheters were connected to pressure transducers which recorded blood pressure for 4 to 8 hours. The animals treated with subcutaneous 0.4 mg/hour GTN patches implanted in the dorsal neck region, showed a 15% decrease in MAP 250 minutes post implantation. Animals treated with a single 30 mg/kg intraperitoneal injection of Losartan showed a 20% decrease in MAP 250 minutes after injection. From these data, treatment protocols for the NMDA infusion experiments shown in Figure 28 were generated.

Example 7

Characterization of neuroreceptor interactions

The direct effects of organic nitrates on amino acid neurotransmitter receptors has been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp recording methods. Human recombinant γ-aminobutyric acid type A ($GABA_A$) receptors composed of α1β2γ2L subunits were expressed in *Xenopus* oocytes as described in Reynolds et al. (1996), incorporated herein by reference. $GABA_A$ receptor-activated membrane current was recorded in individual oocytes, and modulation of this current by GTN and organic nitrates described herein was assessed. GABA (10 μM) was applied until the peak steady-state current response was obtained. IVd (Bunte salt) was pre-applied for 30 seconds prior to exposure of the oocyte to GABA. At 100 μM, IVd produced a 55% inhibition of the response to 10 μM GABA (Fig. 30). This effect appears to be unrelated to the production or release of nitric oxide, as diethylamine nonoate salt (DEA) and *t*-butylnitrosothiol (t-BuSNO) which both spontaneously release nitric oxide in aqueous solution, had no effect on GABA receptor-activated membrane current in an oocyte expressing the α1β2γ2L isoform of the $GABA_A$ receptor. In contrast, nitroglycerin (GTN) produced a reversible inhibition of the GABA response (Fig. 31). Organic nitrates such as GTN and IVd do not compete with GABA for binding to the $GABA_A$ receptor. Rather, they are believed to produce an allosteric modulation of the receptor that decreases the maximal current without changing the apparent affinity of the receptor for GABA. For example, compound IVd (Bunte salt, pre-applied for 30 seconds) decreased the peak current amplitude in an oocyte from 302 nA to 150 nA. However, the EC_{50} concentration (GABA concentration producing 50% of the maximal

response) for GABA was not changed (Fig. 32). Other organic nitrates described herein have been found to have similar inhibitory effects on $GABA_A$ receptor-activated membrane current.

Example 8

Synthesis of IIIe

To acetic anhydride (3 mL) was added gradually, with stirring, 70% nitric acid (0.26 mL), while keeping the temperature between 20-30° by external cooling. With continuous vigorous stirring the mixture was cooled to -30-35° and 2',3'-dideoxy-3-thiocytosine (0.25 g) was added. After 10 min. at -35°, the reaction mixture was heated up to -20° and then stirred at -20-10° for 15 min, and 10 min at 0°. The resulting reaction mixture was poured into ice-water, stirred for 1 hr, then $NaHCO_3$ was added by portions until CO_2 evolution ceased. The water solution was extracted with 3x20 mL of ethyl acetate. Combined extracts were dried ($MgSO_4$) and concentrated. 0.38 g of slightly yellowish oil was obtained. The oil crystallized in a day and was recrystallized from $CHCl_3$. Yield 52%. Conversion to the nitrate was evidenced by the significant downfield shift of the C5' proton multiplet from δ 3.6 to 4.85 ppm.

Example 9

Synthesis of nitrate IIIf

0.26 mL (4.15 mmol) conc. HNO_3 was added to 2 mL acetic anhydride such that the temperature did not exceed 25 – 30 °C. The mixture was cooled at 0 – 5 °C and 0.3 g (1.88 mmol) of 5-(1,2-dihydroxyethyl)-4-methylthiazole was added in several portions, the temperature being kept below 5 °C. The reaction mixture was stirred at 0 – 5 °C for 45 min and then 0.45 mL water was added. The mixture was stirred for 30 min and then rotary evaporated. The residue was neutralized by adding 5 mL of saturated $NaHCO_3$ solution and the organic product was extracted with ethyl acetate. The organic layer was concentrated and the dinitrate IIIf was purified through column chromatography (silica gel/ ethyl acetate eluant). A slightly yellow solid was obtained. Yield: 0.150 g (32 %).

Example 10

Synthesis of nitrate IIIi

Nitrate IIIi was obtained by two routes. Route I proceeded from the elimination reaction of IIIm in basic solution. Route II proceeded from nitration of *trans*-3-bromo-4-hydroxytetrahydrothiophene-1,1-dioxide, yielding nitrate IIIn, followed by reaction with a weak base, e.g., sodium thiocyanate in 2-butanone. Purification is achieved with silica flash column chromatography using 1:1 hexane:ethyl acetate as eluant.

Example 11

Synthesis of nitrate IIIj

1,4-Dibromo-2,3-butanediol is nitrated: (a) using a nitration mixture prepared from HNO_3 and H_2SO_4 over 2 days; or (b) using acetyl nitrate reacting for 2 hours. Work-up requires quenching of the reaction mixture in ice-water for an hour, extraction, drying, and evaporation. Successful purification of the title compound by silica gel column chromatography is achieved on a 25 g scale using a mixture of 70% hexane and 30% CH_2Cl_2 as eluent.

Example 12

Synthesis of nitrate IIIk and IIIl

Synthesis from dinitrate IIIj proceeded by refluxing with sodium or potassium thiocyanate (2 eq.) in 2-butanone for 8 hr. After cooling, a precipitate was removed by filtration and the filtrate was concentrated. Nitrates IIIk and IIIl were separated by silica flash column chromatography with hexane/dichloromethane as eluent.

Example 13

Synthesis of nitrate IIIm

3,4-Epoxytetrahydrothiophene-1,1-dioxide (250 mg,1.9 mmol) was refluxed for 24 hrs in 10 mL of water and 25mg of toluenesulfonic acid. After the first 6 hrs, another 25 mg of

the acid was added. The reaction was monitored by thin layer chromatography (5% MeOH in dichloromethane). Purification was by silica flash column chromatography using 5% MeOH/CH_2Cl_2 as eluent to afford 200 mg of diol. The diol was nitrated in a cooled solution of conc. sulfuric acid (2 mol eq.), nitric acid (70%, 2 mol eq.) in an ice bath. The temperature was maintained as close to 0 °C as possible. The ice bath was removed and the mixture was allowed to stir for 1 hour (reaction was monitored by thin layer chromatography, 100% CH_2Cl_2 eluent). The acid layer was removed and the organic layer washed with: (i) water; (ii) 10% sodium carbonate; (iii) 10% urea; (iv) water. Drying over sodium sulfate, filtration and concentration, yielded crude product which was purified by flash column chromatography, with dichloromethane as eluent. An alternative route involves direct nitration of 3,4-epoxytetrahydrothiophene-1,1-dioxide in a similar nitration mixture.

Example 14

Synthesis of nitrate IVk

1.17 mL (18.2 mmol) concentrated HNO_3 was added, under stirring and cooling (0 – 5 °C), to 1 mL (18.2 mmol) concentrated H_2SO_4 and then 2 g (14 mmol) of 4-methyl-5-(2-hydroxyethyl)thiazole was added dropwise into the nitration mixture, the temperature being kept under 10 °C. The mixture was stirred for 3 hours at room temperature, diluted with 10 mL of water and neutralized with solid $NaHCO_3$. The organic product was extracted with ethyl acetate and purified by column chromatography (silica gel/ ethyl acetate eluant) to produce a colorless oily product. Yield: 1.18 g (45%).

Example 15

Synthesis of nitrate Ivi

0.03 g (0.035 ml) of allyl cyanide was added to a stirred suspension of 0.22 g (0.5 mmol) of Tl $(NO_3)_3.3H_2O$ in 2 mL of pentane. After 20 min of vigorous stirring, the pentane solution was decanted and evaporated to dryness. After evaporation the residual oil (0.44 g) was columned (CH_2Cl_2, Rf 0.64 (CH_2Cl_2). Clean oil immediately crystallized during an attempt to dissolve it in $CDCl_3$. Yield 0.065 g (76%). The structure of IVn was confirmed by

X-ray analysis. IR (film): 1297.03, 1678.91, 2258.91 (CN). Mass spec. m/z (CI^+ fragment, %): 191.9 (M+H, 2.44), 129.0 (16.41), 81.9 (100). Calculated for $C_4H_5N_3O_6$ 191.02.

Example 16

Synthesis of nitrate IVn

0.9 g (0.75 mL, 4.92 mmol) of allyphenyl sulfone was added dropwise to a stirred suspension of 2.43 g (5.47 mmol) of Tl $(NO_3)_3.3H_2O$ in 10 mL of pentane. The resulting mixture was stirred overnight. The pentane solution was decanted. 2x10 mLl of MeOH (methanol) were added to the reaction mixture, stirred for 10 minutes and extracts were added to the pentane solution. The combined extracts were evaporated to dryness and purified by silica flash column chromatography using CH_2Cl_2 as eluant. Yield 0.08 g (15%). IR (KBr): 1152.39, 1290.91, 1273.12, 1353.83, 1646.08. Mass spec. m/z (CI^+ fragment, %): 307.0 (M+1, 66.5), 244.0 (100%). Calculated for $C_9H_{10}N_2O_8S$ 306.02.

Example 17

Synthesis of nitrate Va

2.2 g (7.3 mmol) of nitrate IVd was dissolved in 5 g of cold H_2O_2 (30%, 0°C) and then 1 g of 10 % H_2SO_4 was added. The mixture was stirred at 0-5 °C until a white oil separated (ca. 30-60 min). The aqueous layer was discarded and the oil was dissolved in dichloromethane, washed successively with water, then $NaHCO_3$ solution and finally water. The organic solution was dried over $MgSO_4$. Removal of the solvent produced 1.3 g of the crude product which was purified by column chromatography (Silicagel, CH_2Cl_2/hexanes : 70/30). Yield: 0.650 g (45 %).

Example 18

Synthesis of nitrate Vc.

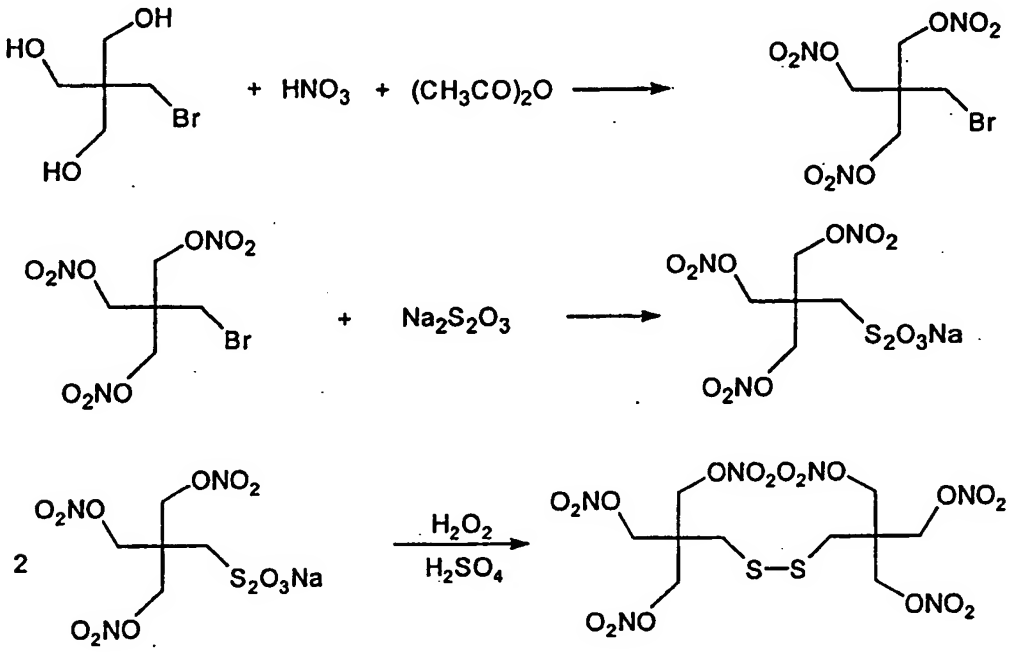
3 g (8.88 mmol) of 1,4-dibromo-2,3-dinitrobutanediol and 2.81 g (18 mmol) of $Na_2S_2O_3.5H_2O$ were dissolved in a mixture of 100 mL of MeOH and 45 mL of H_2O. The resulting solution was heated during 4 days at 40-45°. After this time the reaction mixture was

partially evaporated to reduce the volume of solvents. The resulting mixture was extracted 4x50 mL of ethyl ether. The extracts were combined, washed (H_2O), dried ($MgSO_4$) and evaporated to minimum. Column chromatography afforded the title compound in 10% yield, separated from Vb, the major product.

Example 19

Synthesis of nitrate IIIh

The synthetic route employed for synthesis of the hexanitrate IIIh is shown in the Scheme:



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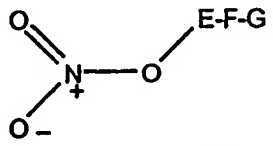
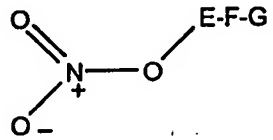
What is claimed is:

1. A method for effecting cognition enhancement in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cognition enhancement occurs, wherein the therapeutic compound has the formula (Formula I):



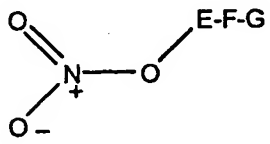
wherein E, F, G are organic radicals which may contain inorganic counterions.

2. A method for mitigating cellular damage due to ischemia in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cellular damage is mitgated, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions.

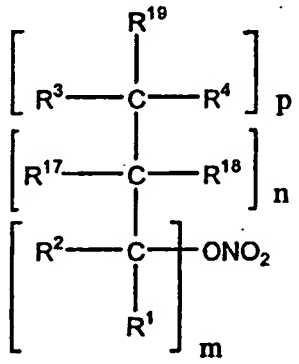
3. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions,

with the proviso that when E is methylene, F and G are not both C_1 organic radicals each bearing one nitrate group.

4. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a

substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3 are nitrate groups;

that R^4 is not H or C_1 – C_3 alkyl.

5. The method of claim 4, wherein:

R^{19} is X-Y.

6. The method of claim 5, wherein:

R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains, which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R^5);

R^7, R^{11} are the same or different C_1 – C_8, alkyl or acyl;

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

7. The method of claim 6, wherein:

m = 1, n = 0, p=1.

8. The method of claim 7, wherein:

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SSR^4; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist.

9. The method of claim 6, wherein:

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, SR^4 or SSR^5, or does not exist.

10. The method of claim 3, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

11. The method of claim 3, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

12. The method of claim 3, wherein administering the therapeutic compound to the subject modulates an activity of the glutamate neuroreceptor.

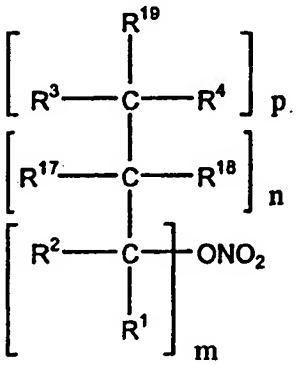
13. The method of claim 3, wherein administering the therapeutic compound to the subject modulates an activity of a non-glutamate neuroreceptor.

14. The method of claim 3, wherein administering the therapeutic compound to the subject modulates cerebral guanylyl cyclase activity.

15. The method of claim 3, wherein administering the therapeutic compound to the subject modulates apoptosis.

16. The method of claim 3, wherein administering the therapeutic compound to the subject modulates cerebral free radical damage.

17. A method for treating a disease state associated with neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that a disease state associated with neurodegeneration is treated, wherein the therapeutic compound has the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages

(e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3 are nitrate groups;

that R^4 is not H or C_1 – C_3 alkyl.

18. The method of claim 17, wherein:

R^{19} is X-Y.

19. The method of claim 18, wherein:

R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains, which may inlude one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R^5);

R^7, R^{11} are the same or different C_1 – C_8, alkyl or acyl;

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

20. The method of claim 19, wherein:

m = 1, n = 0, p=1.

21. The method of claim 20, wherein:

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SSR^4; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist.

22. The method of claim 20, wherein:

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

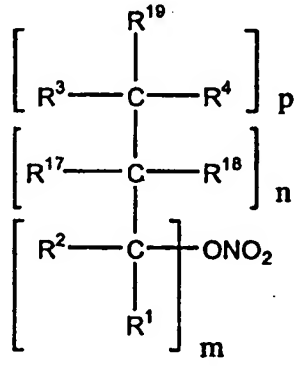
Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, SR^4 or SSR^5, or does not exist.

23. The method of claim 2, wherein administering the therapeutic compound to the subject modulates levels of cyclic nucleotide cGMP and/or cAMP.

24. The method of claim 17, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

25. The method of claim 17 further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

26. A method for effecting neuroprotection in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that neuroprotection occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n and p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3 are nitrate groups;

that R^4 is not H or C_1 – C_3 alkyl.

27. The method of claim 26, wherein:

R^{19} is X-Y.

28. The method of claim 27, wherein:

R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains which may inlude one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R^5);

R^7, R^{11} are the same or different C_1 – C_8, alkyl or acyl;

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

29. The method of claim 28, wherein:

m = 1, n = 0, p=1.

30. The method of claim 29, wherein:

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SSR^4; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist.

31. The method of claim 28, wherein:

R^5, R^6, R^8 R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

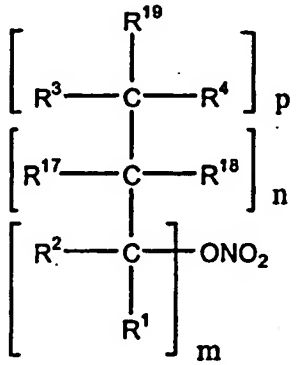
X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, SR^4 or SSR^5, or does not exist.

32. The method of claim 26, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

33. The method of claim 26, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

34. A method for effecting cognition enhancement in a subject comprising administering to said subject an effective amount of a organic nitrate, or therapeutically acceptable salt thereof, having the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen, or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M,

SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3 are nitrate groups;

that R^4 is not H or C_1 – C_3 alkyl.

35. The method of claim 34, wherein:

R^{19} is X-Y.

36. The method of claim 35, wherein:

R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains which may inlude one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cycohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-$C(O)R^5$);

R^7, R^{11} are the same or different C_1 – C_8, alkyl or acyl;

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

37. The method of claim 36, wherein:

m = 1, n = 0, p=1;

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SSR^4; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, SSR^5, or does not exist.

38. The method of claim 36, wherein:

m=1, n=0, p=1;

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

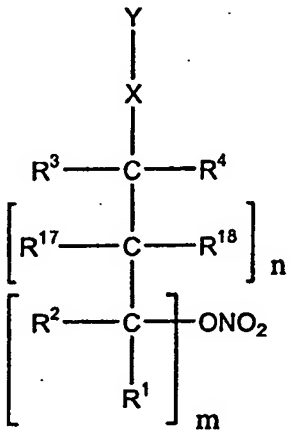
Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, SR^4 or SSR^5, or does not exist.

39. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein guanylyl cyclase is activated and cGMP level is increased.

40. The method of claim 34, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

41. The method of claim 34, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

42. Organic nitrates containing at least one nitrate group having the general formula (Formula III):



in which: m is an integer from 1 to 10; n is an integer from 0 to 10;

$R^{3,4,17}$ are each independently hydrogen, a nitrate group, or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally contains O, S, NR^6 and unsaturations in the linkage,

and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR^6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 - C_6 connections to R^1 – R^4 in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}{}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that,

when m=0; n=1;

R^{18} and R^3 are the same or different and selected from H, a nitrate group, $C_1 - C_4$ alkyl and chains, which may include one O, linking R^{18} and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^{17} and R^4, are the same or different and selected from H, a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (-$C(O)R^5$);

R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^{18},R^{17}, or R^3 in cyclic derivatives;

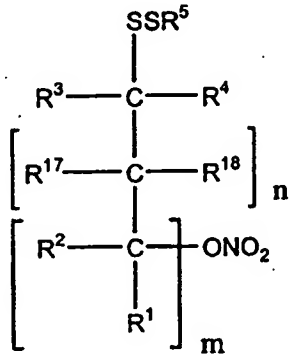
R^7, R^{11} are $C_1 - C_8$ alkyl or acyl;

M is H, Na^+, K^+, NH_4^+, $N^+H_kR^{11}{}_{(4-k)}$ where k is 0-3;

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, or SSR^4;

that Y is not CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SO_2M, PO_3M_2, PO_3HM, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^4, SR^5, or SSR^5, or does not exist.

43. A method for preparing a compound represented by the formula (Formula V):



in which m, n = 0 – 10;

R^4 is hydrogen, a nitrate group, or A;

R^3, R^{17}, R^{18} are each independently hydrogen or A;

and R^5 is A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR_6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR_6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R_1 and R_3 and/or between R_2 and R_4, which optionally contains O, S, NR_6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR_6 and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

the method comprising:

reacting an appropriate halo-alcohol with a nitrating reagent selected from a mixture of nitric and sulfuric acid in a mixture of water and a selected organic solvent, acetyl nitrate, nitronium tetrafluoroborate, or reacting an appropriate halo-alkene with thallium nitrate in pentanes, under conditions such that an appropriate halo-organic nitrate is formed;

reacting an appropriate halo-organic nitrate with a thiolsulfonate salt so as to produce a selected Bunte salt;

reacting an appropriate Bunte salt, optionally with an oxidizing agent (e.g. 30% hydrogen peroxide) in the presence of an appropriate catalyst (e.g. sulfuric acid), under conditions such that the compound of Formula 5 is prepared;

reacting an appropriate disulfide in a thiol/disulfide exchange reaction with an organic thiolate salt, under conditions such that a compound of Formula 5 is formed.

44. The method of claim 2, wherein administering the therapeutic compound to the subject modulates cellular free radical damage.

FIGURE 1

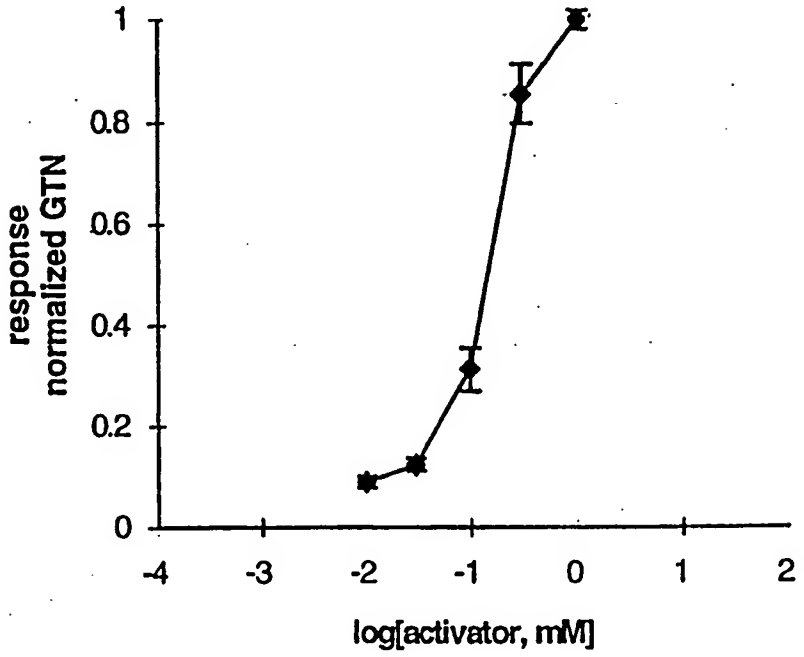

response
normalized GTN
1
0.8
0.6
0.4
0.2
0
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 2

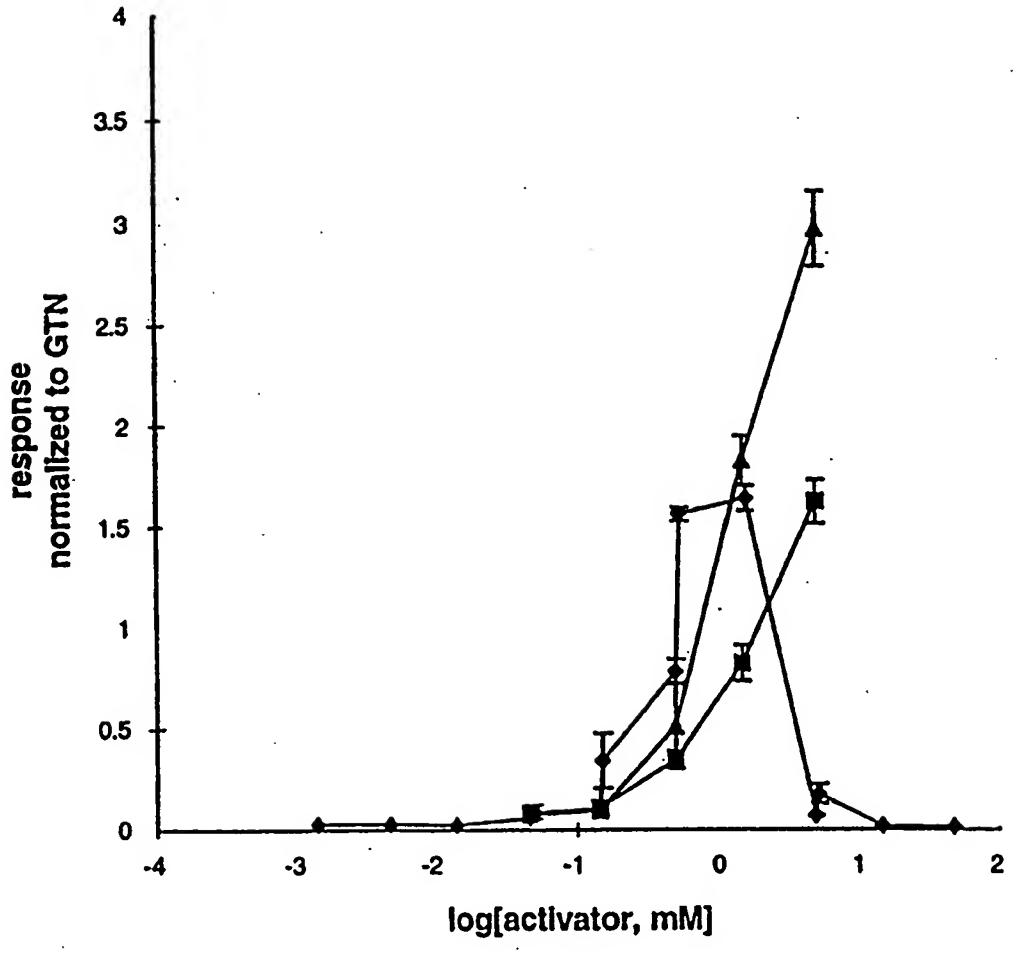

response normalized to GTN
4
3.5
3
2.5
2
1.5
1
0.5
0
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 3

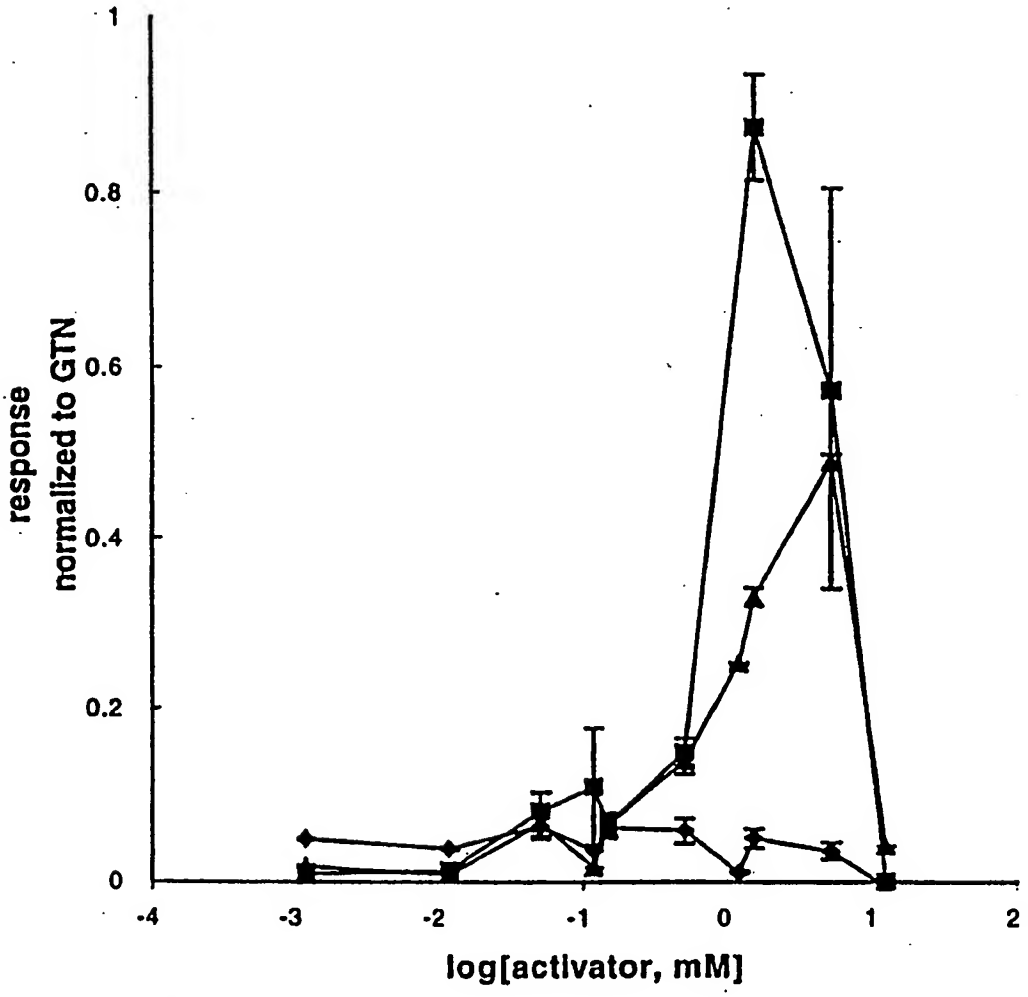

response
normalized to GTN
1
0.8
0.6
0.4
0.2
0
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 4

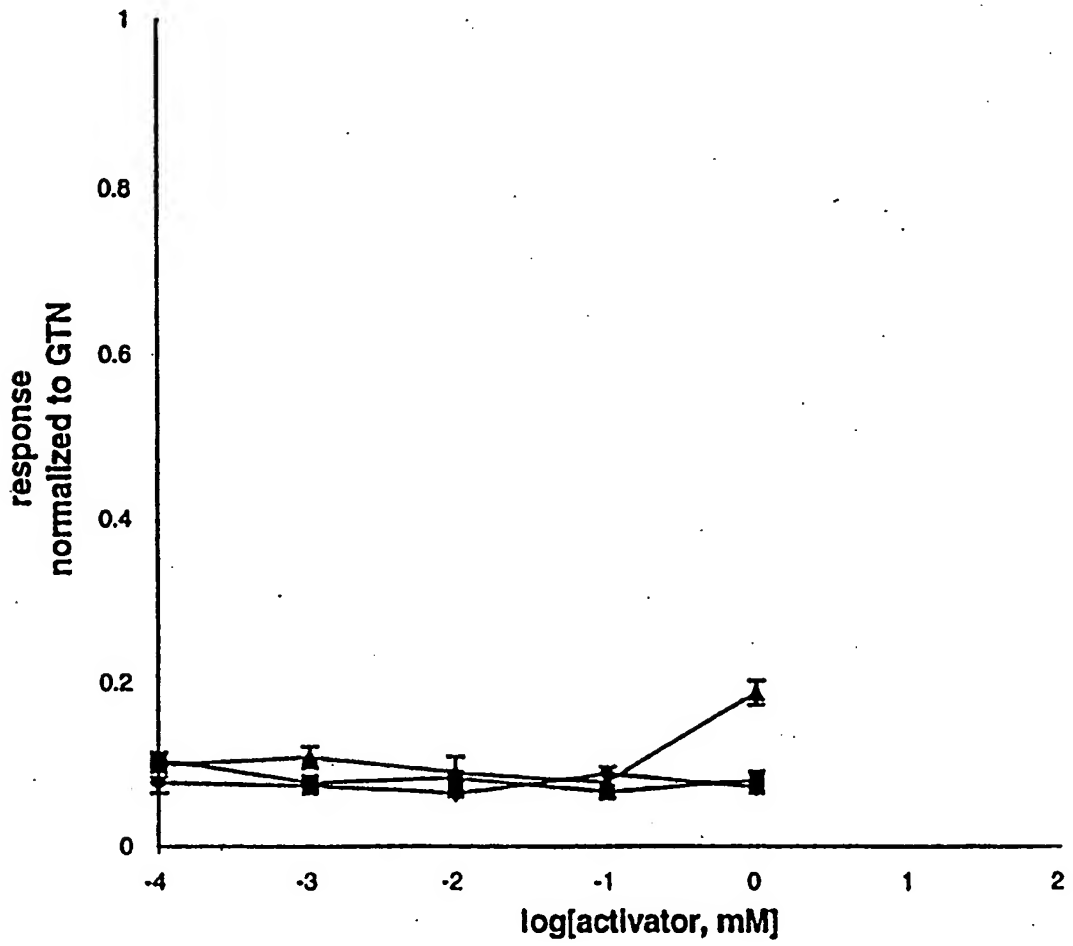

1
0.8
0.6
0.4
0.2
0
response
normalized to GTN
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 5

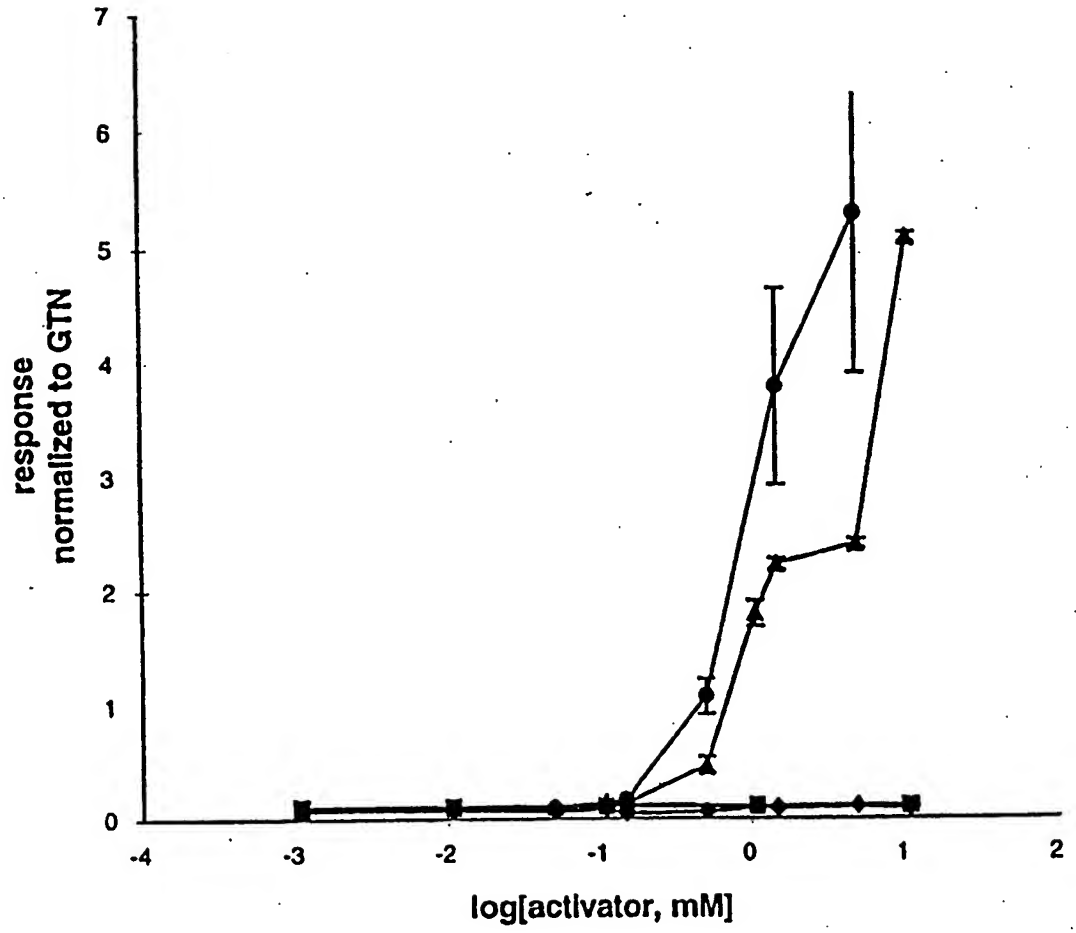

response
normalized to GTN
7
6
5
4
3
2
1
0
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 6

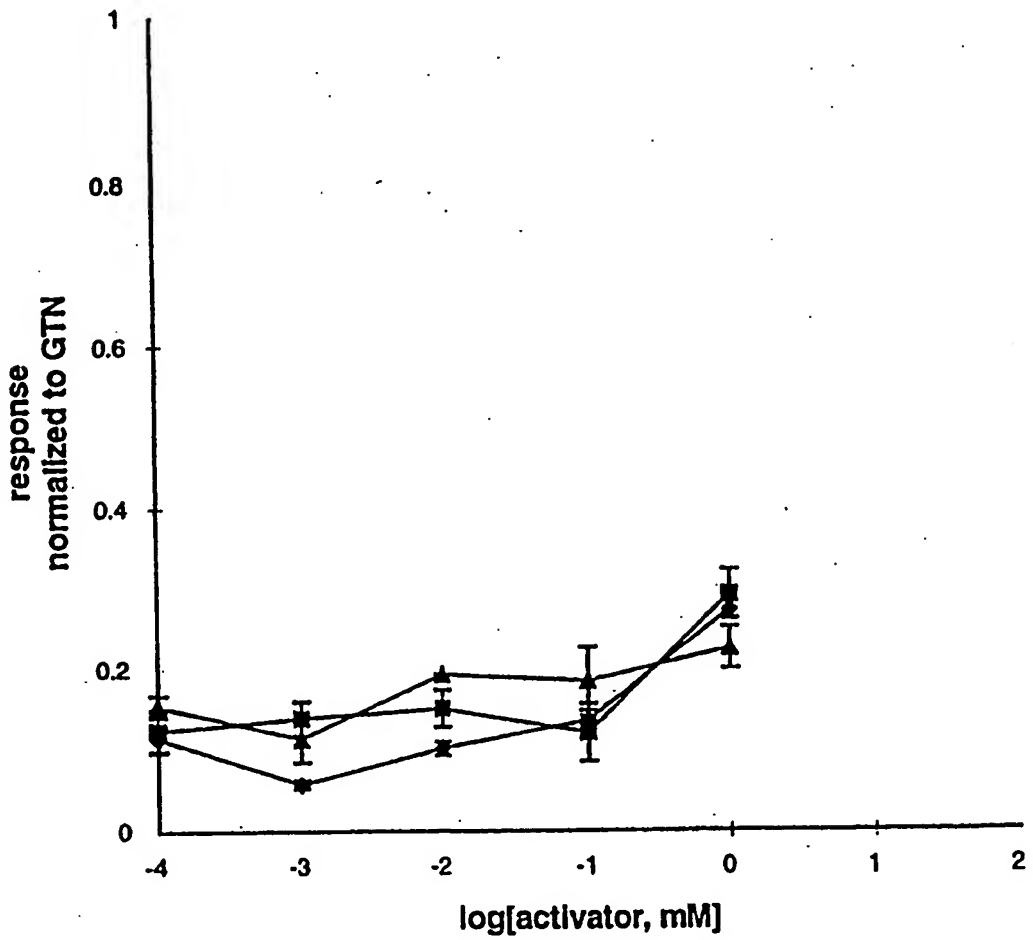

1
0.8
0.6
0.4
0.2
0
response
normalized to GTN
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE.7

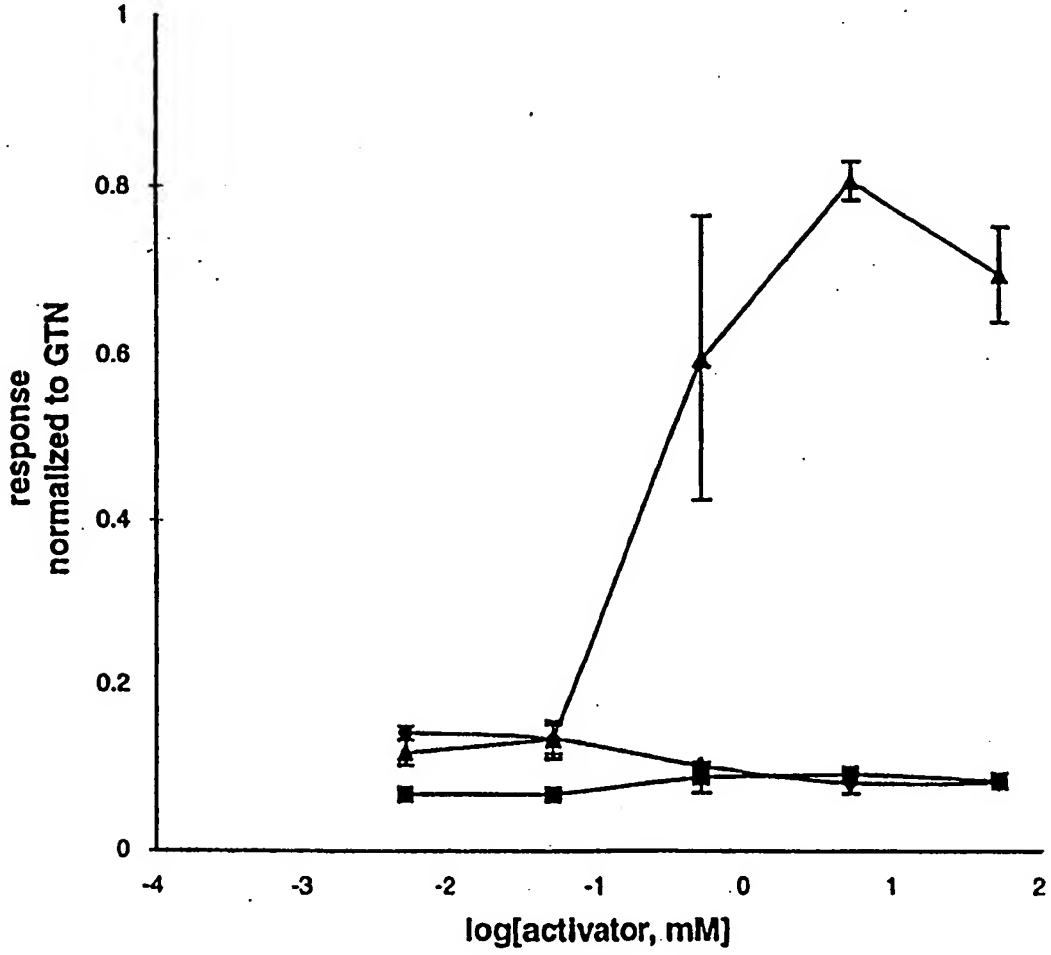

response normalized to GTN
1
0.8
0.6
0.4
0.2
0
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 8

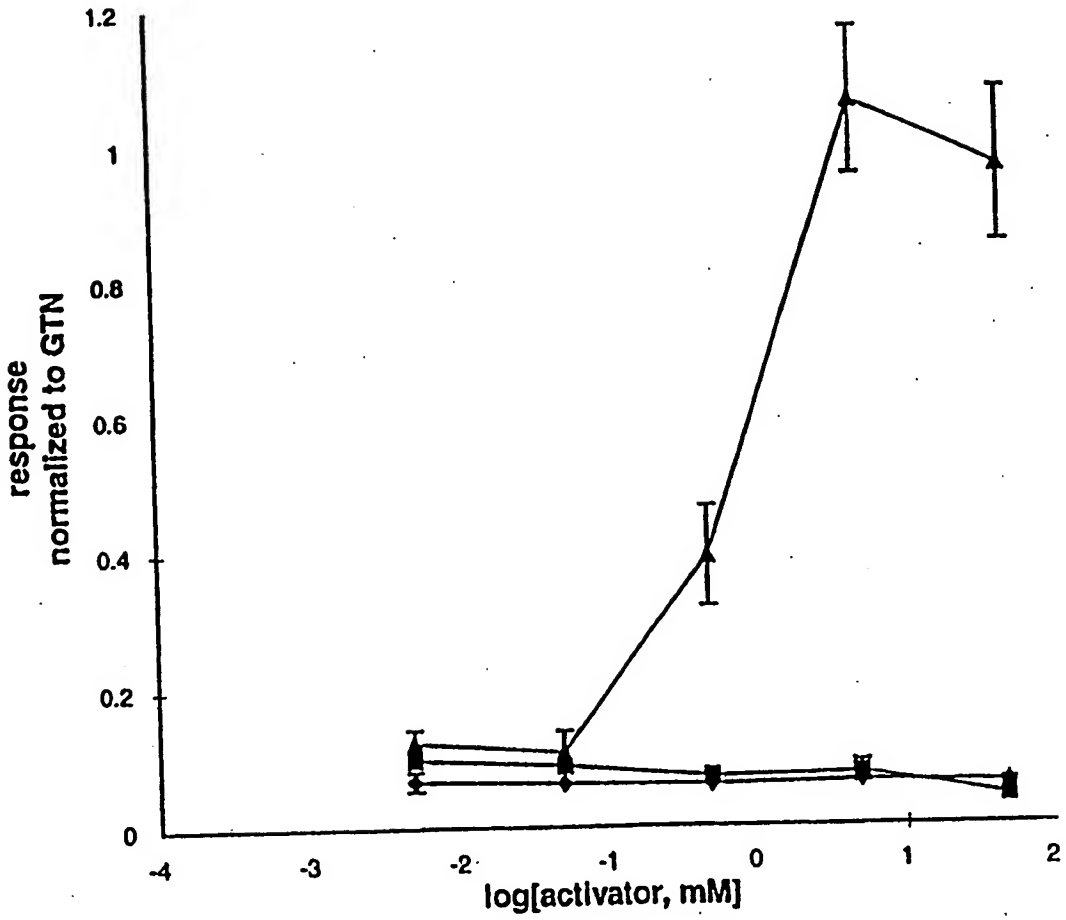

1.2
1
0.8
0.6
0.4
0.2
0
response
normalized to GTN
-4
-3
-2
-1
0
1
2
log[activator, mM]

FIGURE 9

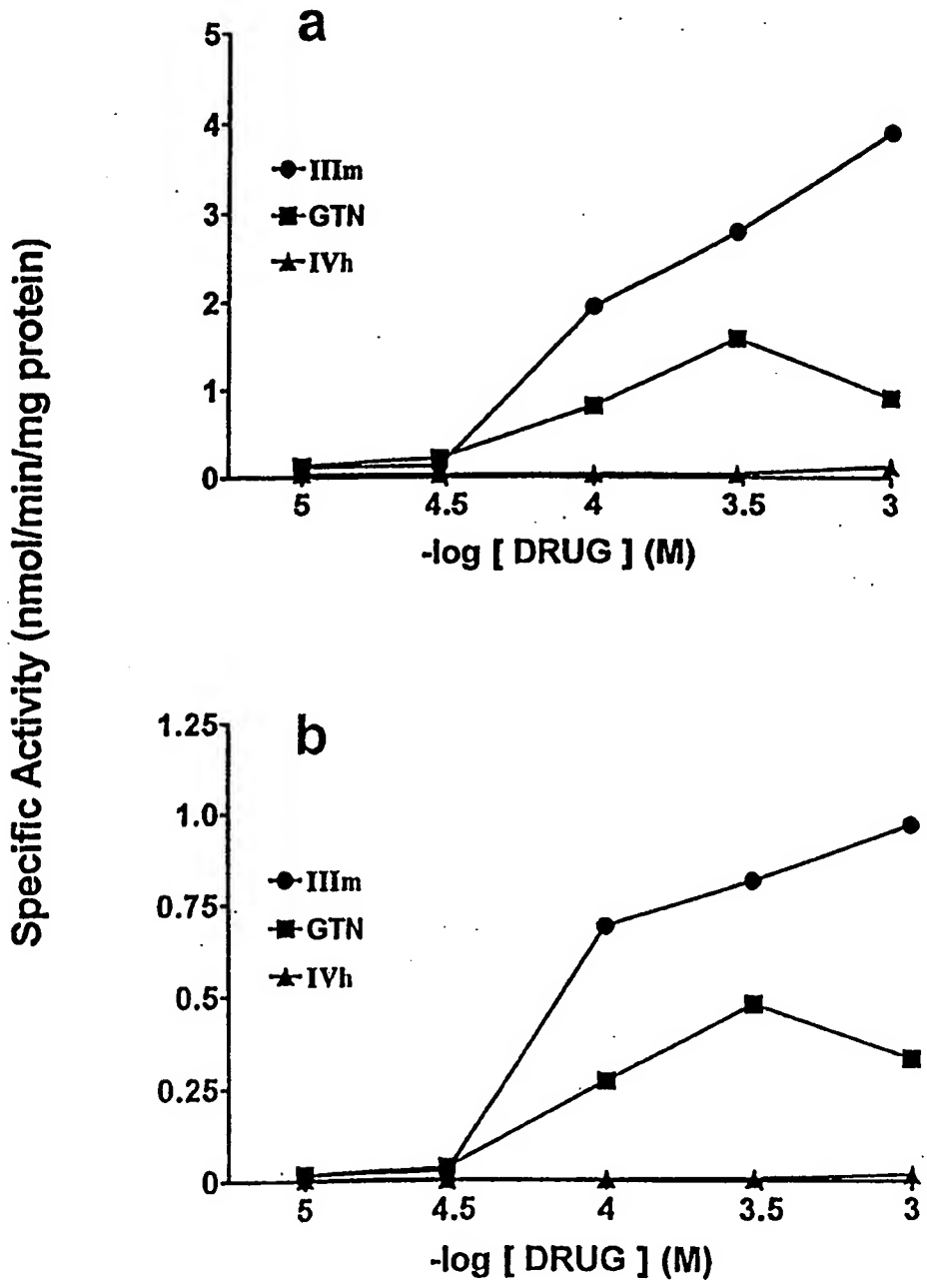

a
b
IIIm
GTN
IVh
Specific Activity (nmol/min/mg protein)
-log [DRUG] (M)
5
4.5
4
3.5
3
0
0.25
0.5
0.75
1.0
1.25

FIGURE 10

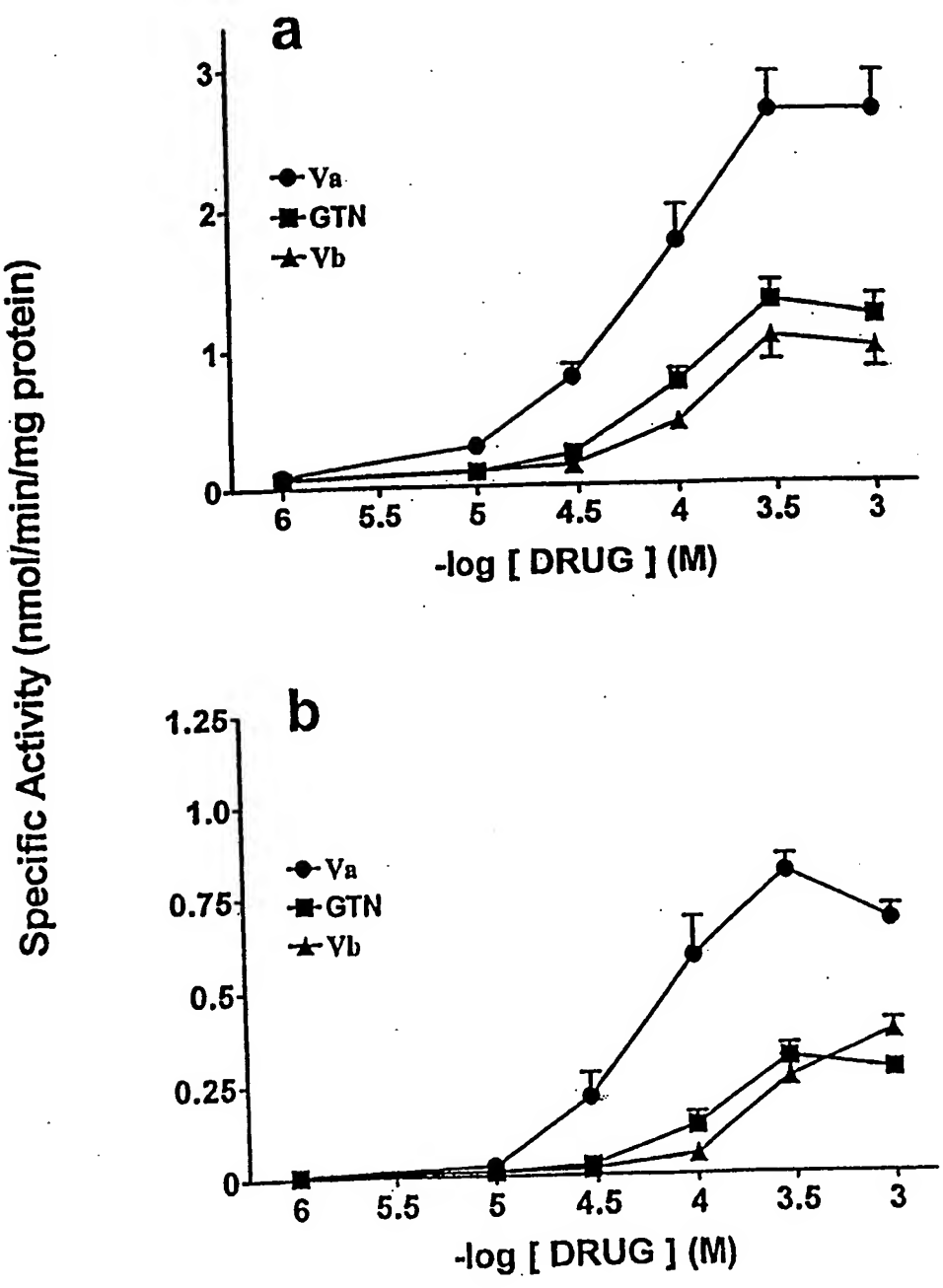

a
b
Va
GTN
Vb
Specific Activity (nmol/min/mg protein)
-log [DRUG] (M)
0
1
2
3
0.25
0.5
0.75
1.0
1.25
6
5.5
5
4.5
4
3.5
3

FIGURE 11

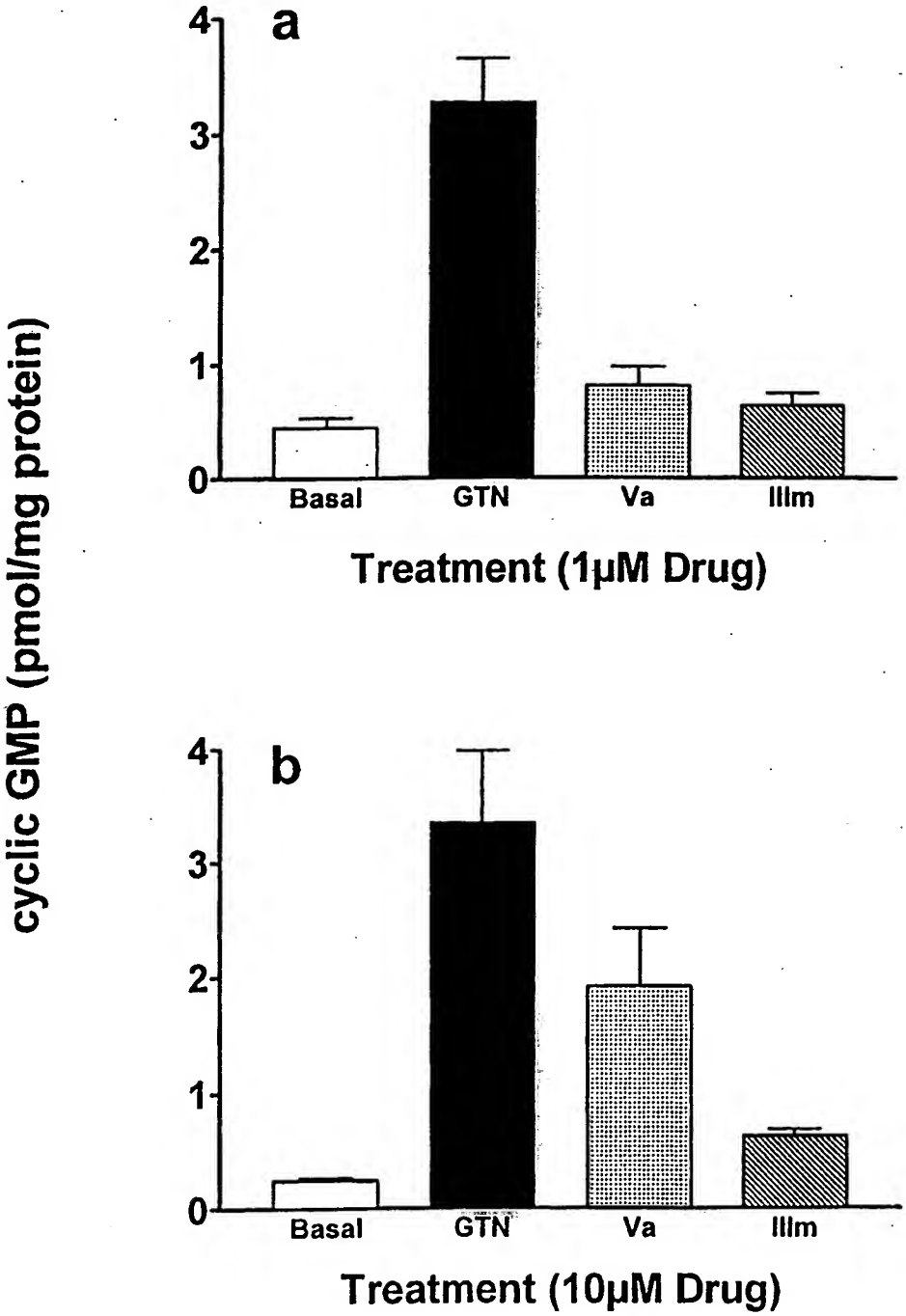

a
4
3
2
1
0
Basal
GTN
Va
IIIm
Treatment (1µM Drug)
cyclic GMP (pmol/mg protein)
b
4
3
2
1
0
Basal
GTN
Va
IIIm
Treatment (10µM Drug)

FIGURE 12

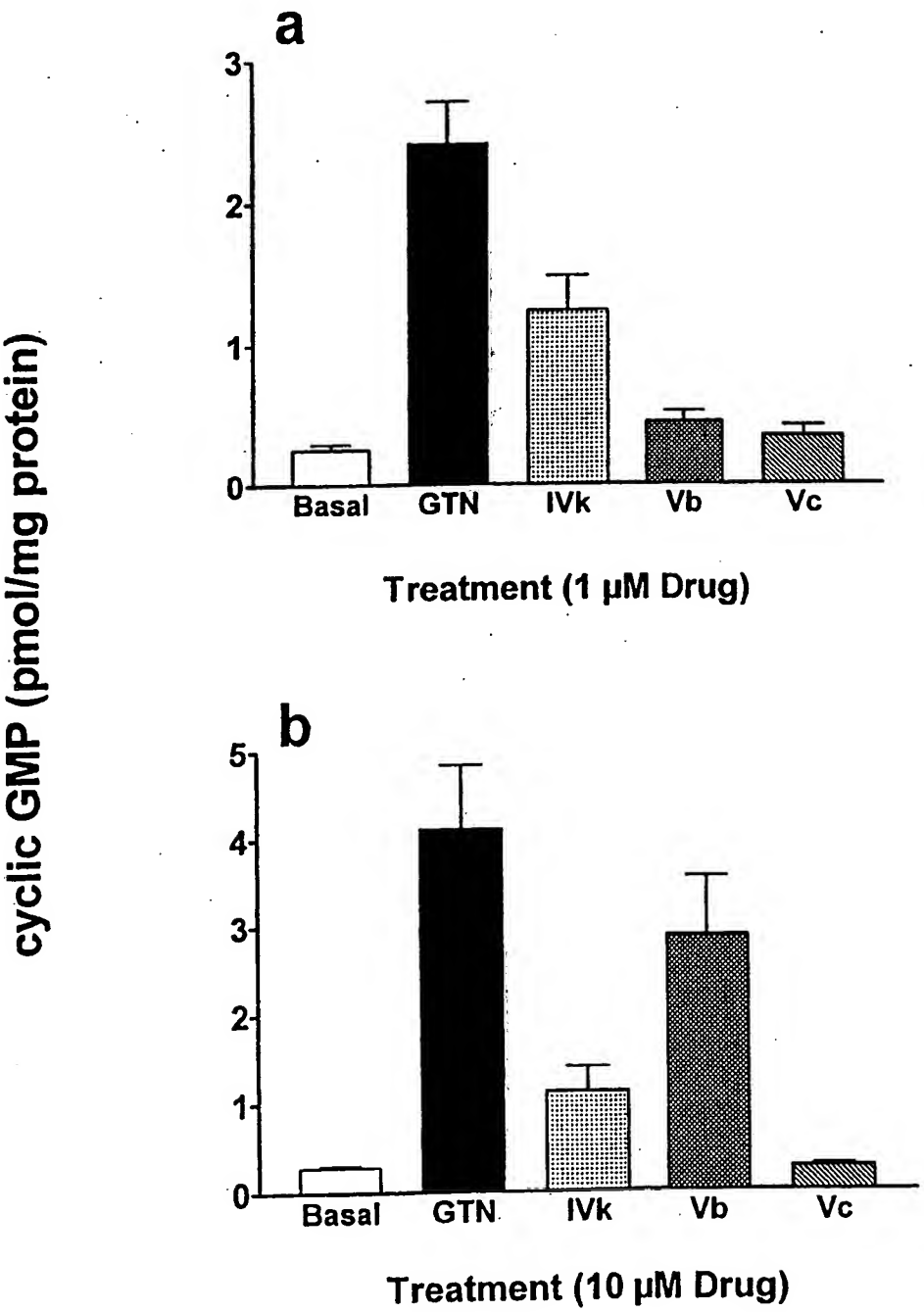

a
3
2
1
0
Basal
GTN
IVk
Vb
Vc
Treatment (1 µM Drug)
cyclic GMP (pmol/mg protein)
b
5
4
3
2
1
0
Basal
GTN
IVk
Vb
Vc
Treatment (10 µM Drug)

FIGURE 13

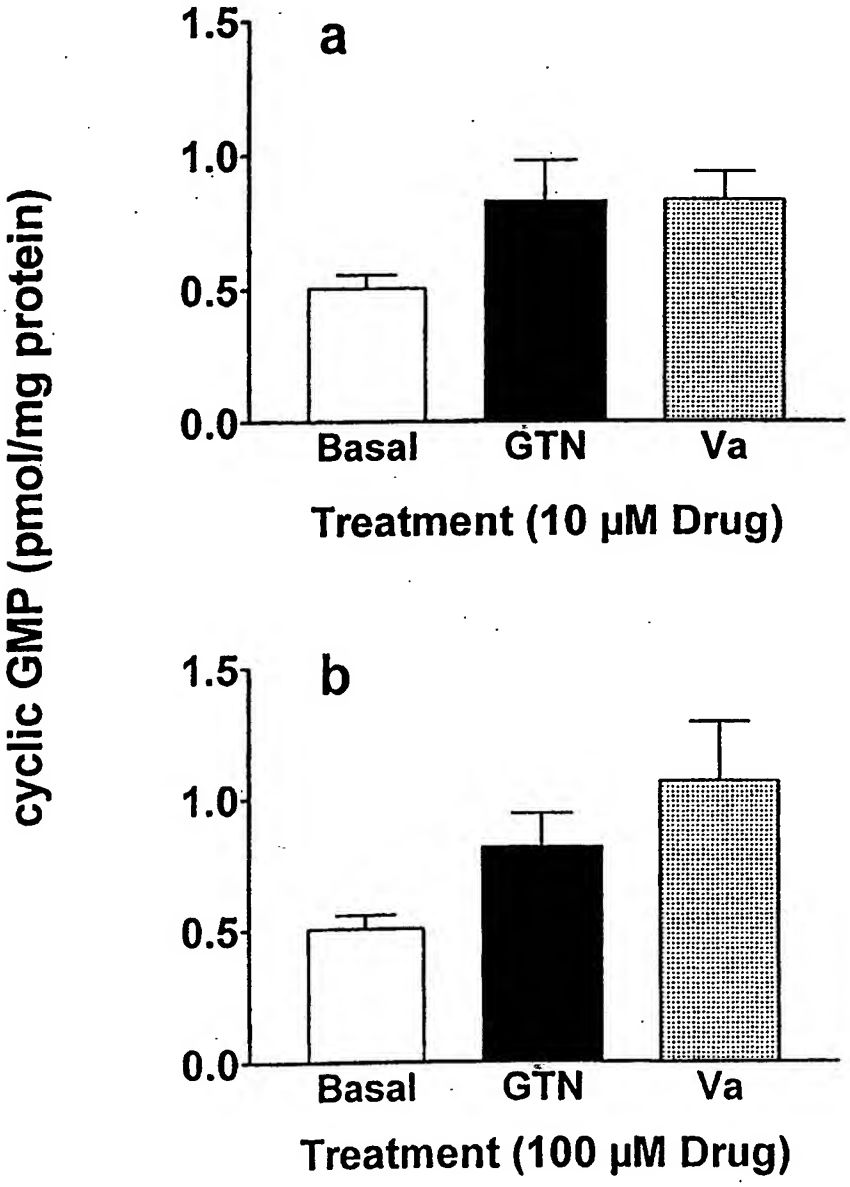

a
1.5
1.0
0.5
0.0
Basal
GTN
Va
Treatment (10 µM Drug)
cyclic GMP (pmol/mg protein)
b
1.5
1.0
0.5
0.0
Basal
GTN
Va
Treatment (100 µM Drug)

FIGURE 14

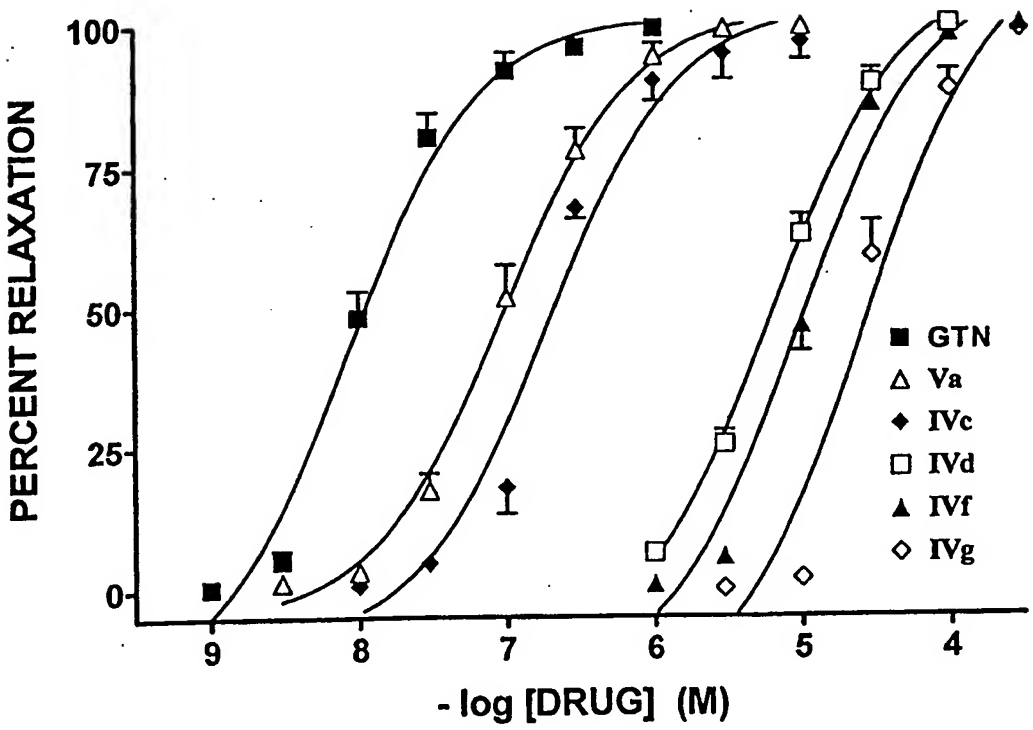

PERCENT RELAXATION
100
75
50
25
0
9
8
7
6
5
4
- log [DRUG] (M)
GTN
Va
IVc
IVd
IVf
IVg

FIGURE 15

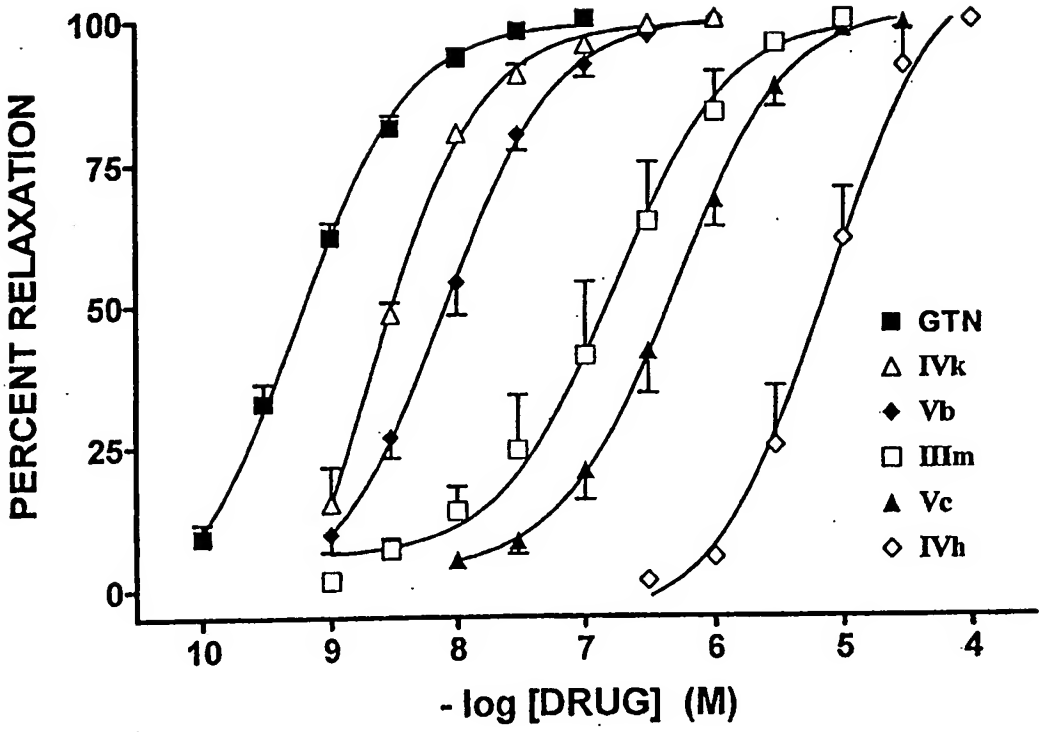

PERCENT RELAXATION
100
75
50
25
0
10
9
8
7
6
5
4
- log [DRUG] (M)
GTN
IVk
Vb
IIIm
Vc
IVh

FIGURE 16

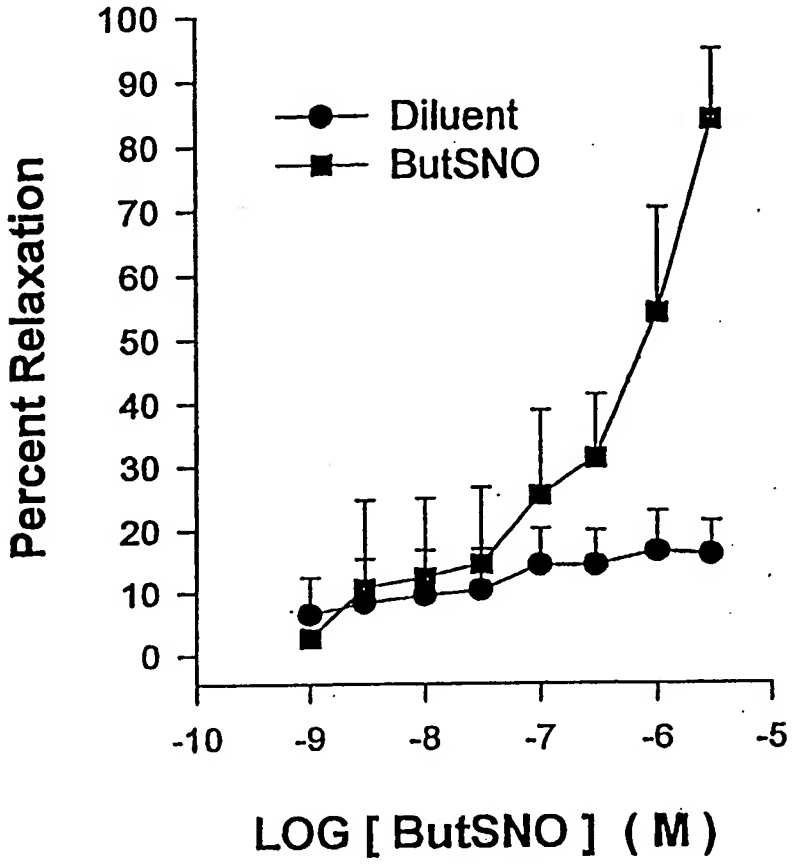
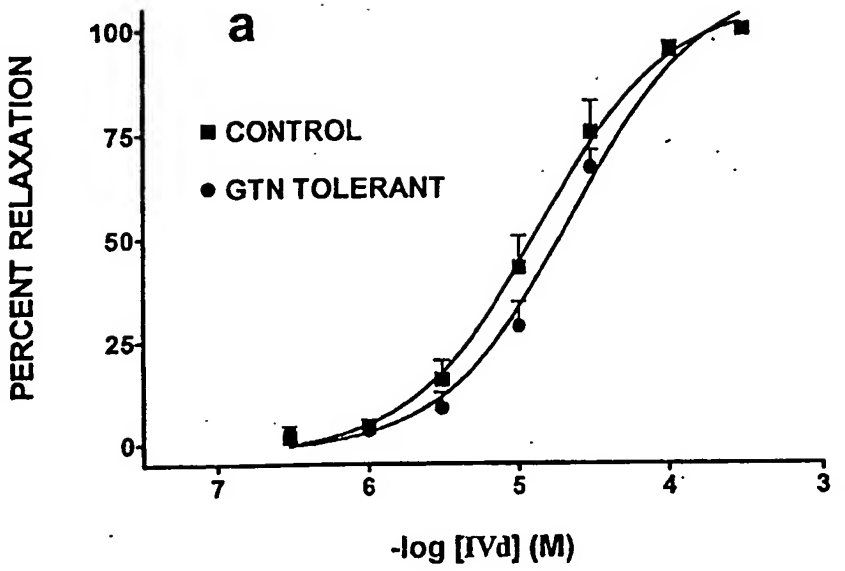

100
90
80
70
60
50
40
30
20
10
0
Percent Relaxation
Diluent
ButSNO
-10
-9
-8
-7
-6
-5
LOG [ButSNO] (M)

FIGURE 17


a
100
75
50
25
0
PERCENT RELAXATION
CONTROL
GTN TOLERANT
7
6
5
4
3
-log [IVd] (M)

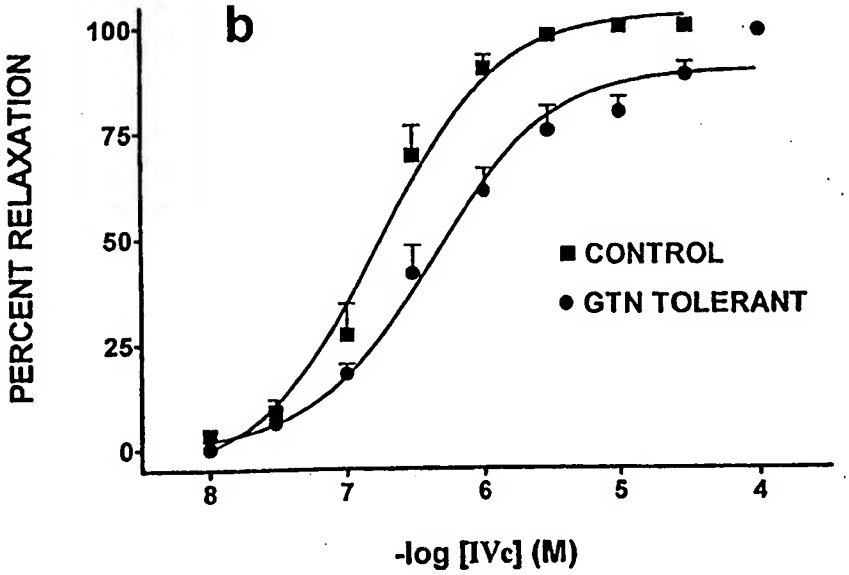

b
100
75
50
25
0
PERCENT RELAXATION
CONTROL
GTN TOLERANT
8
7
6
5
4
-log [IVc] (M)

FIGURE 18

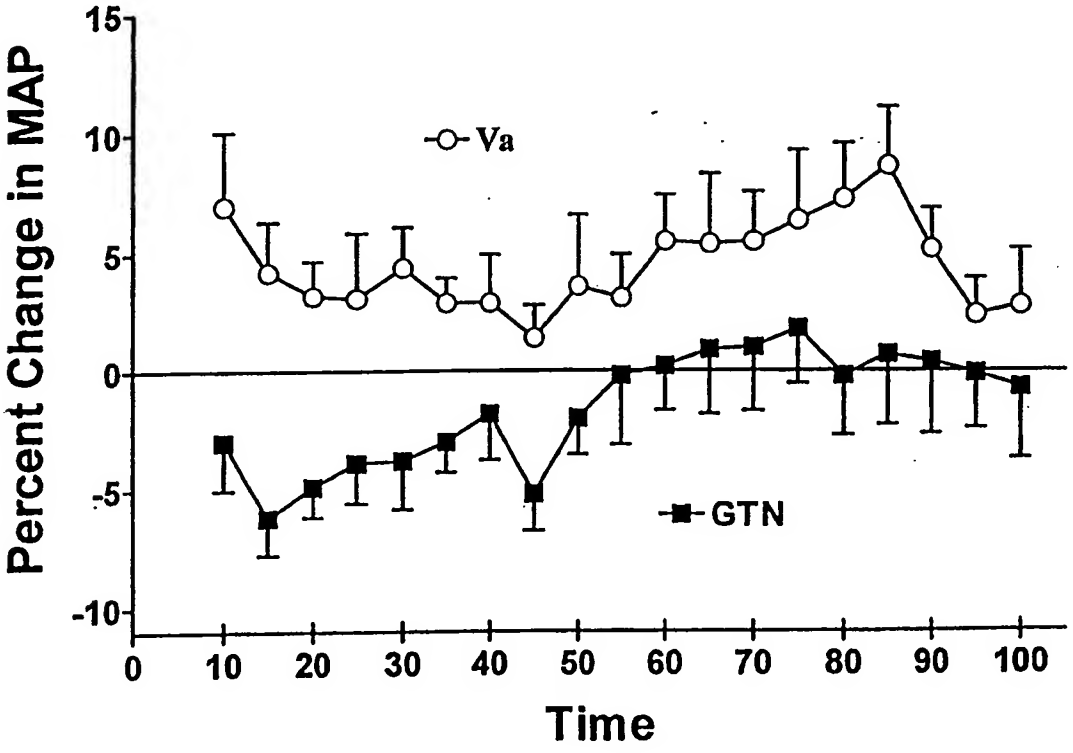

Percent Change in MAP
15
10
5
0
-5
-10
Va
GTN
0
10
20
30
40
50
60
70
80
90
100
Time

FIGURE 19

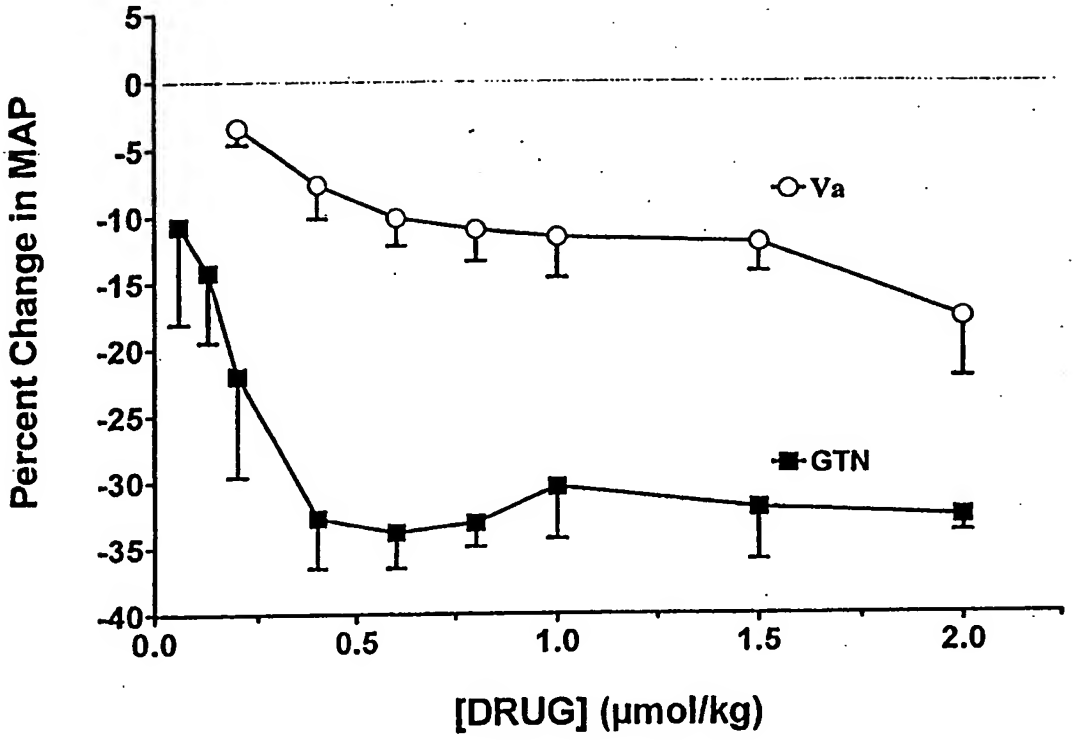

Percent Change in MAP
5
0
-5
-10
-15
-20
-25
-30
-35
-40
0.0
0.5
1.0
1.5
2.0
[DRUG] (µmol/kg)
Va
GTN

FIGURE20

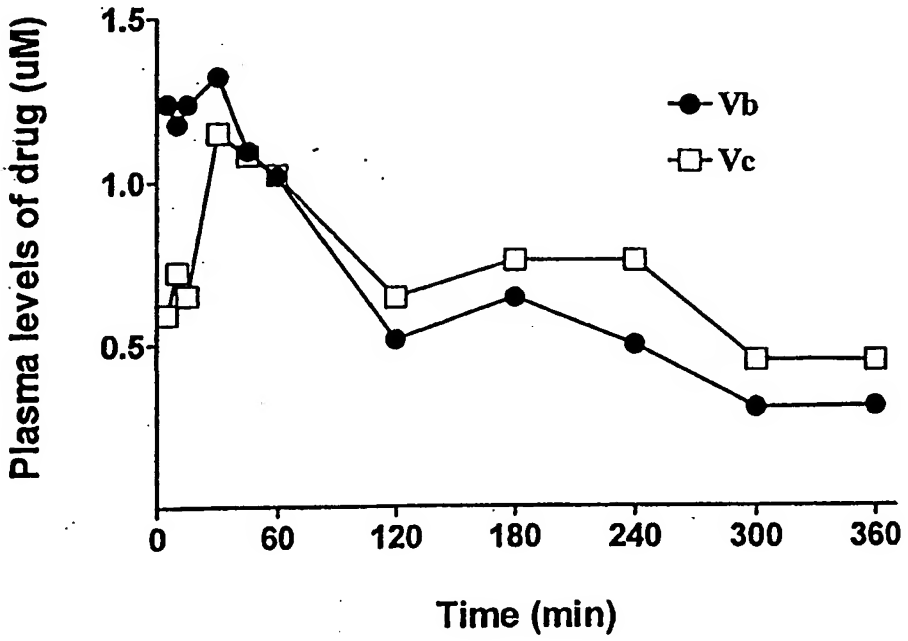

Plasma levels of drug (uM)
1.5
1.0
0.5
0
60
120
180
240
300
360
Time (min)
Vb
Vc

FIGURE 21

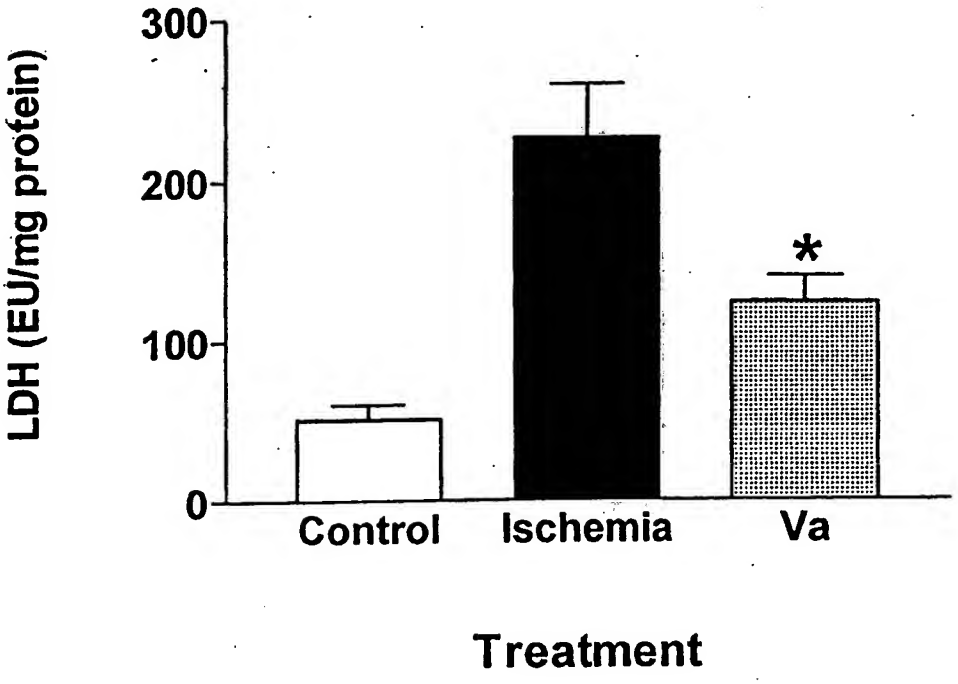

LDH (EU/mg protein)
300
200
100
0
*
Control
Ischemia
Va
Treatment

FIGURE 22

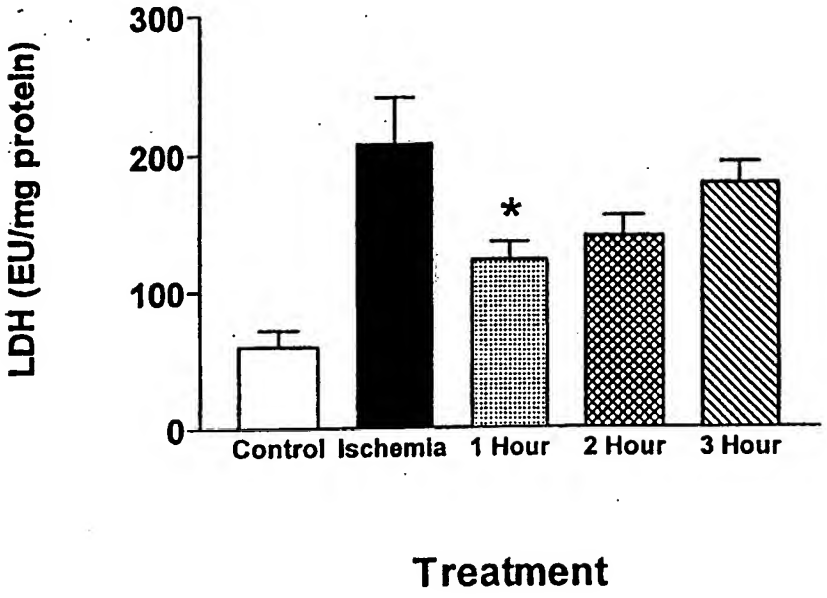

LDH (EU/mg protein)
300
200
100
0
*
Control
Ischemia
1 Hour
2 Hour
3 Hour
Treatment

FIGURE 23

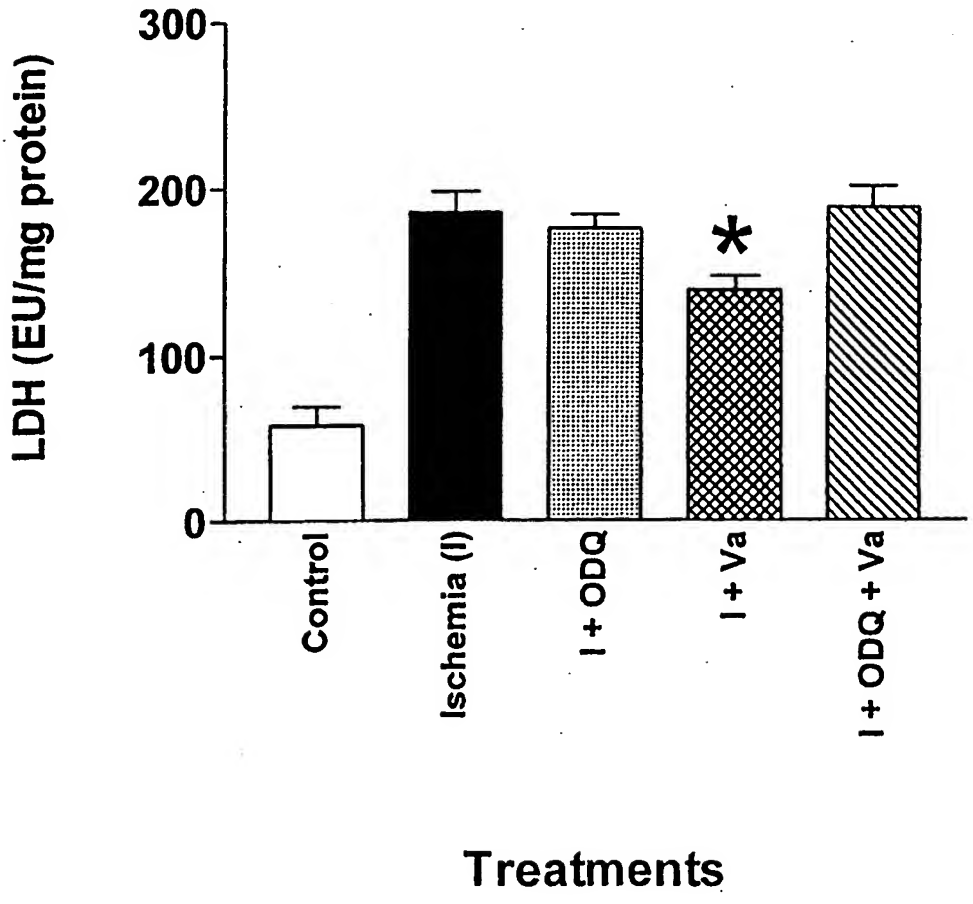

LDH (EU/mg protein)
300
200
100
0
*
Control
Ischemia (I)
I + ODQ
I + Va
I + ODQ + Va
Treatments

FIGURE 24

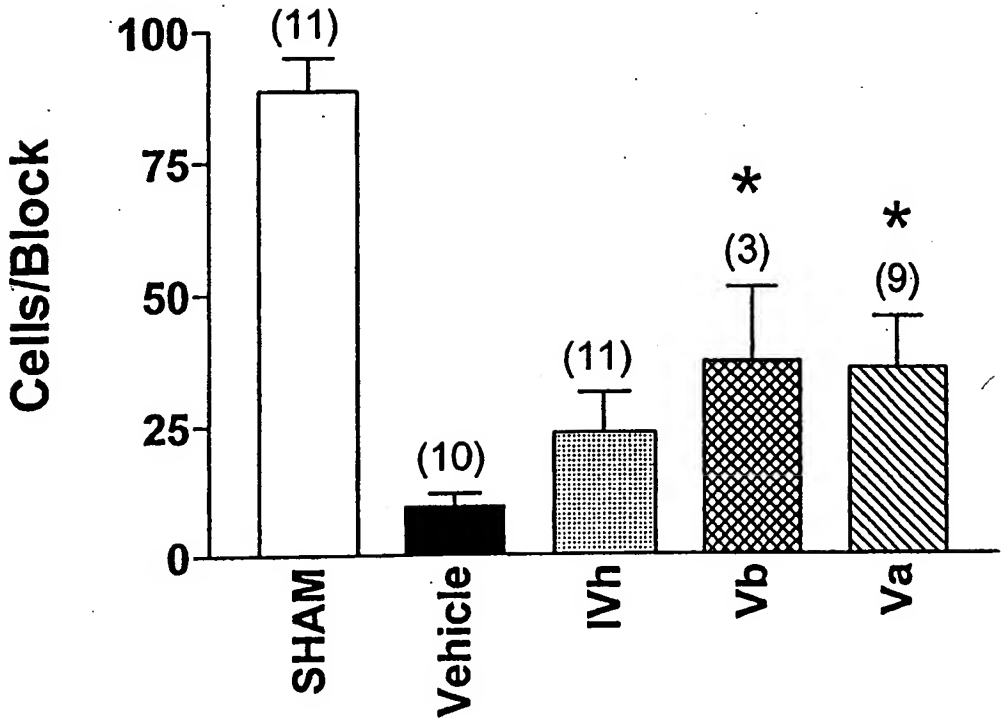
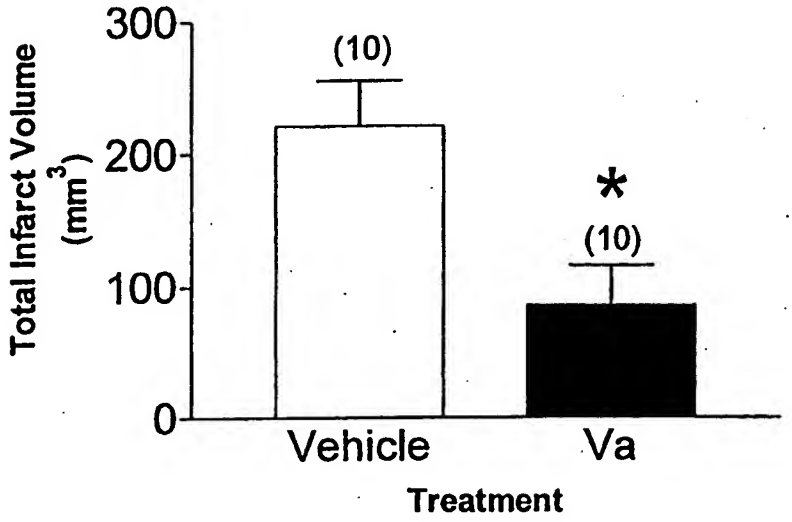


FIGURE 25


300
200
100
0
Total Infarct Volume
(mm3)
(10)
*
(10)
Vehicle
Va
Treatment

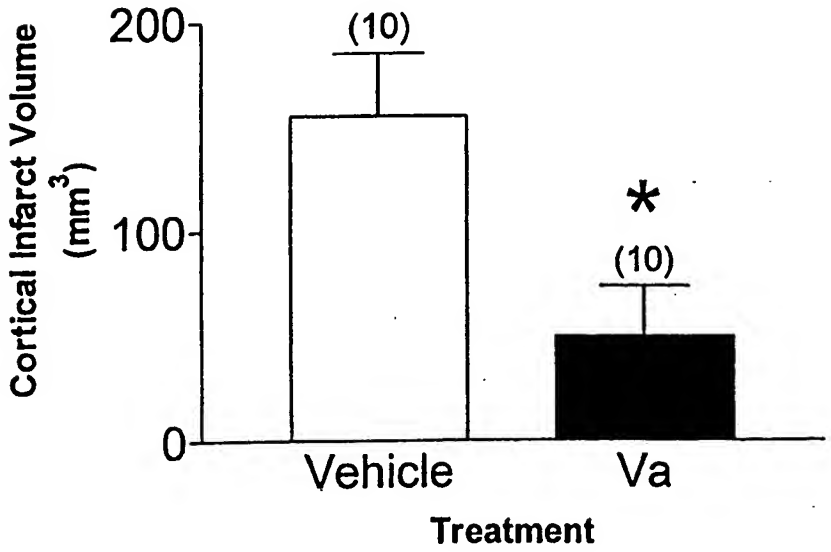

200
100
0
Cortical Infarct Volume
(mm3)
(10)
*
(10)
Vehicle
Va
Treatment

FIGURE 26

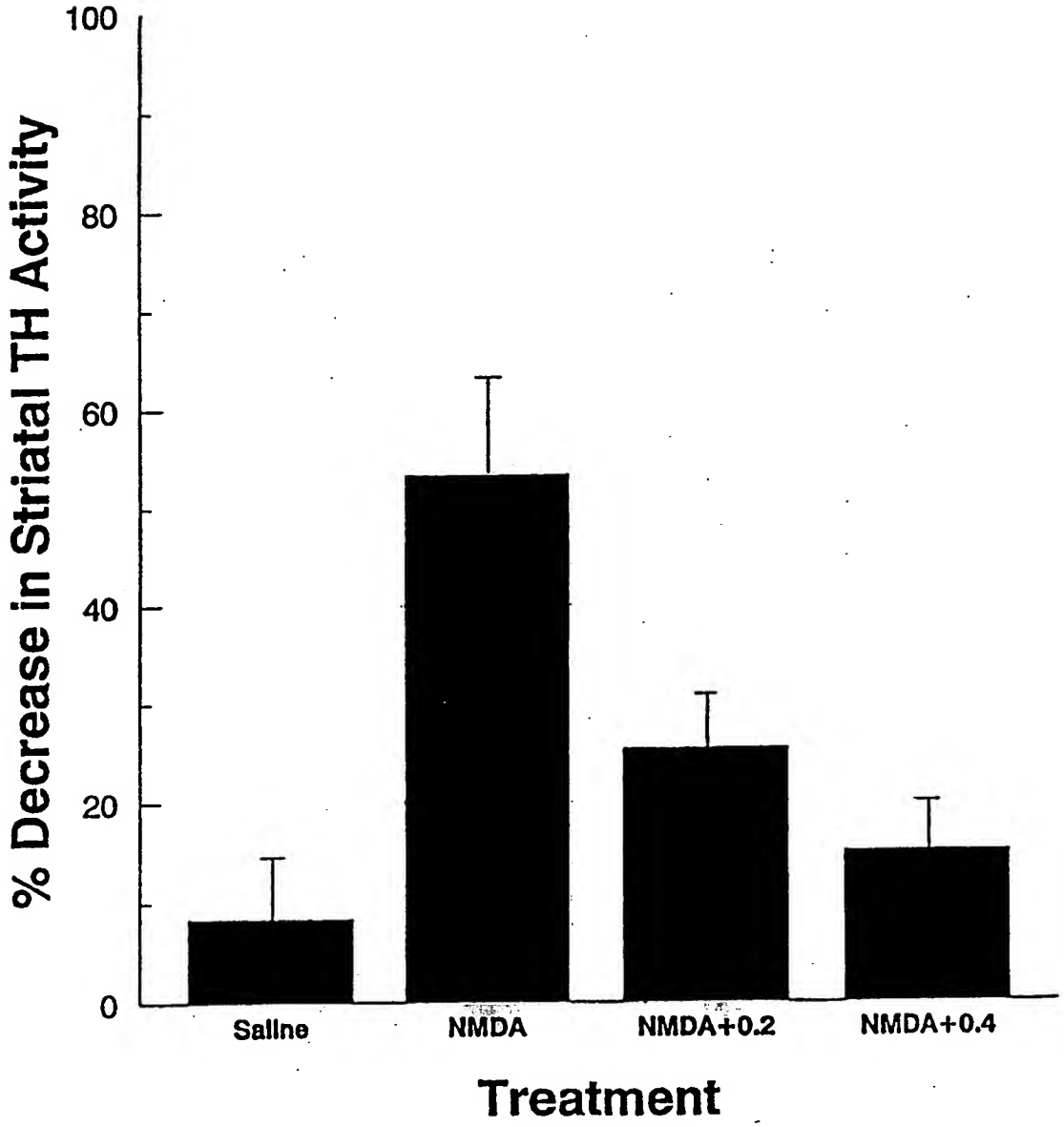

100
80
60
40
20
0
% Decrease in Striatal TH Activity
Saline
NMDA
NMDA+0.2
NMDA+0.4
Treatment

FIGURE 27

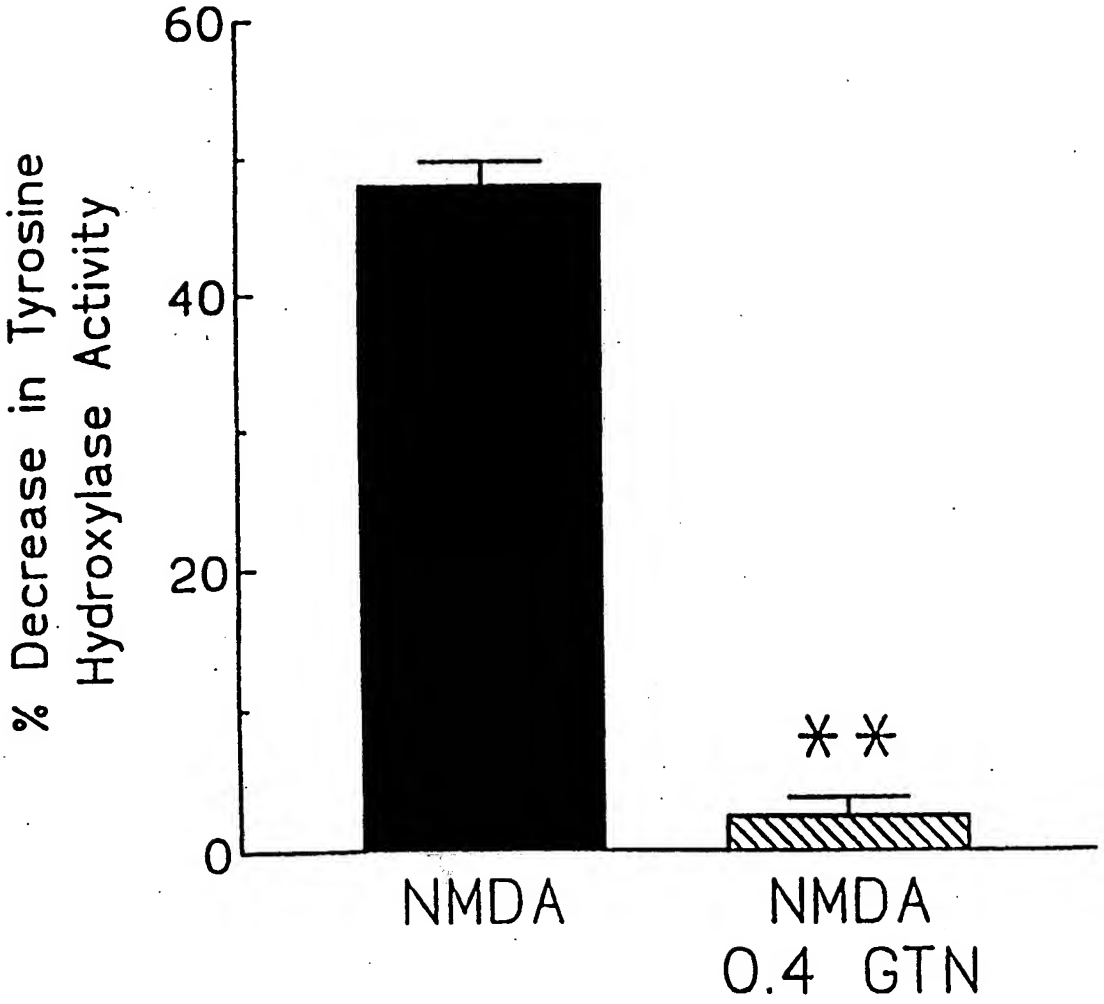

60
40
20
0
% Decrease in Tyrosine Hydroxylase Activity
**
NMDA
NMDA 0.4 GTN

FIGURE 28

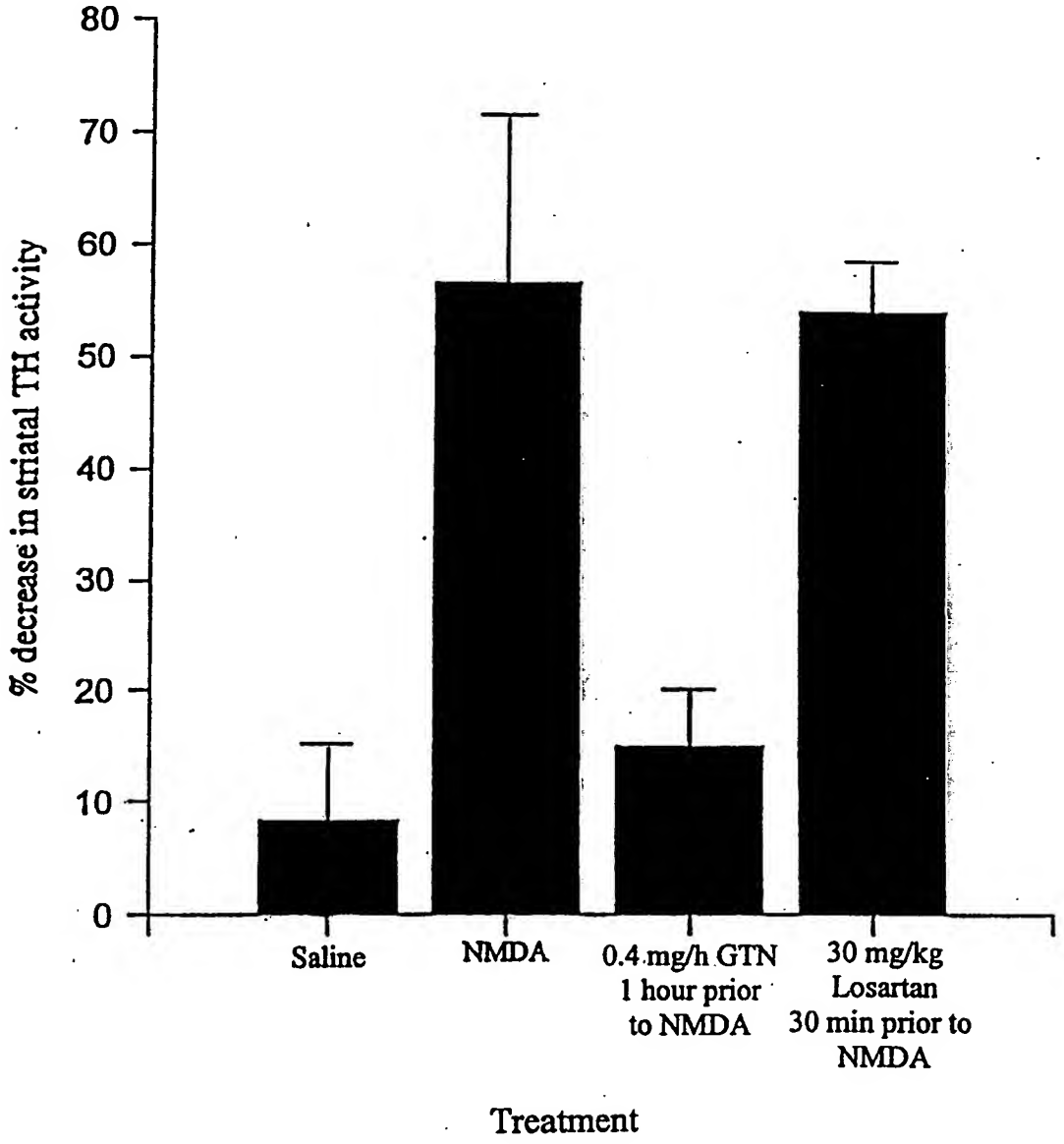

80
70
60
50
40
30
20
10
0
% decrease in striatal TH activity
Saline
NMDA
0.4 mg/h GTN 1 hour prior to NMDA
30 mg/kg Losartan 30 min prior to NMDA
Treatment

FIGURE 29

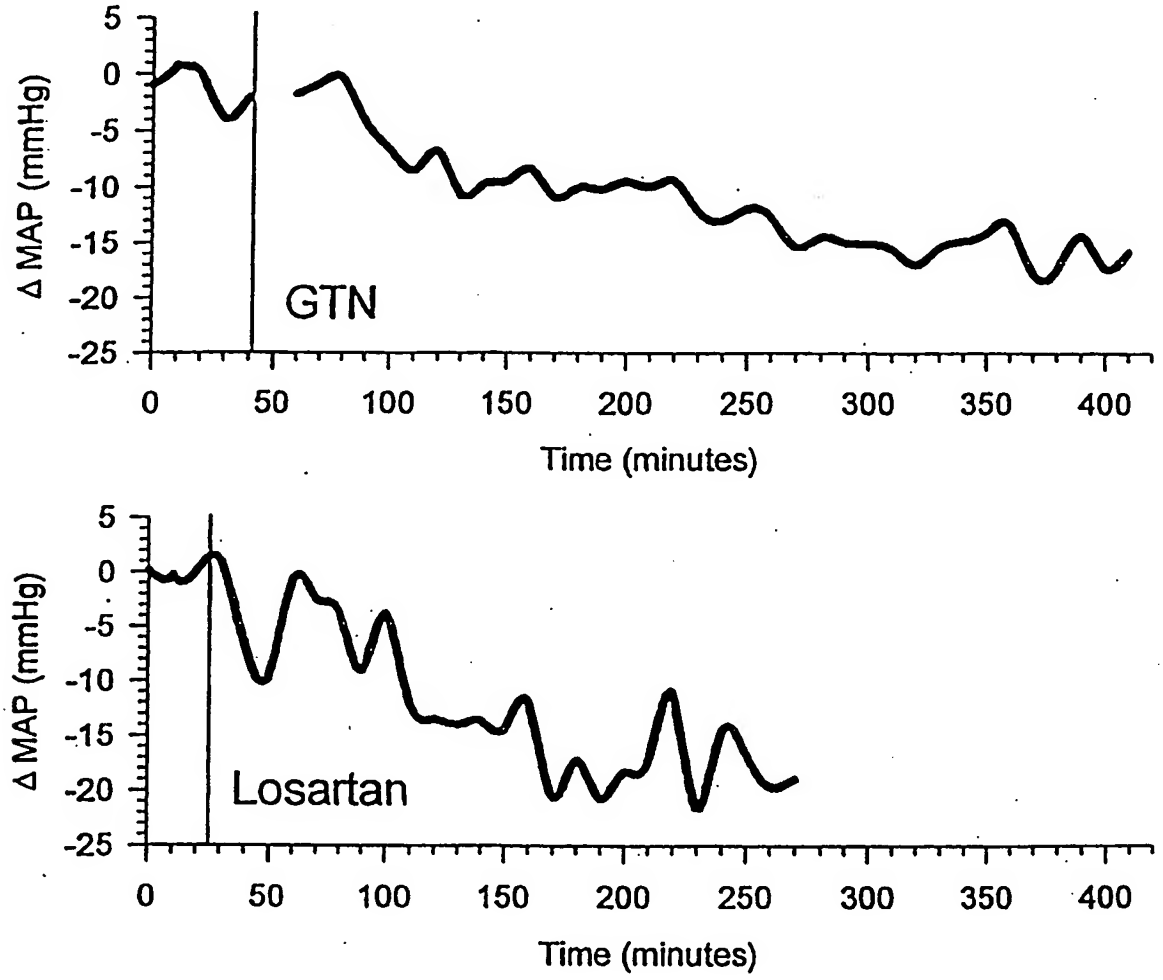

5
0
-5
-10
-15
-20
-25
Δ MAP (mmHg)
GTN
0
50
100
150
200
250
300
350
400
Time (minutes)
5
0
-5
-10
-15
-20
-25
Δ MAP (mmHg)
Losartan
0
50
100
150
200
250
300
350
400
Time (minutes)

FIGURE 30

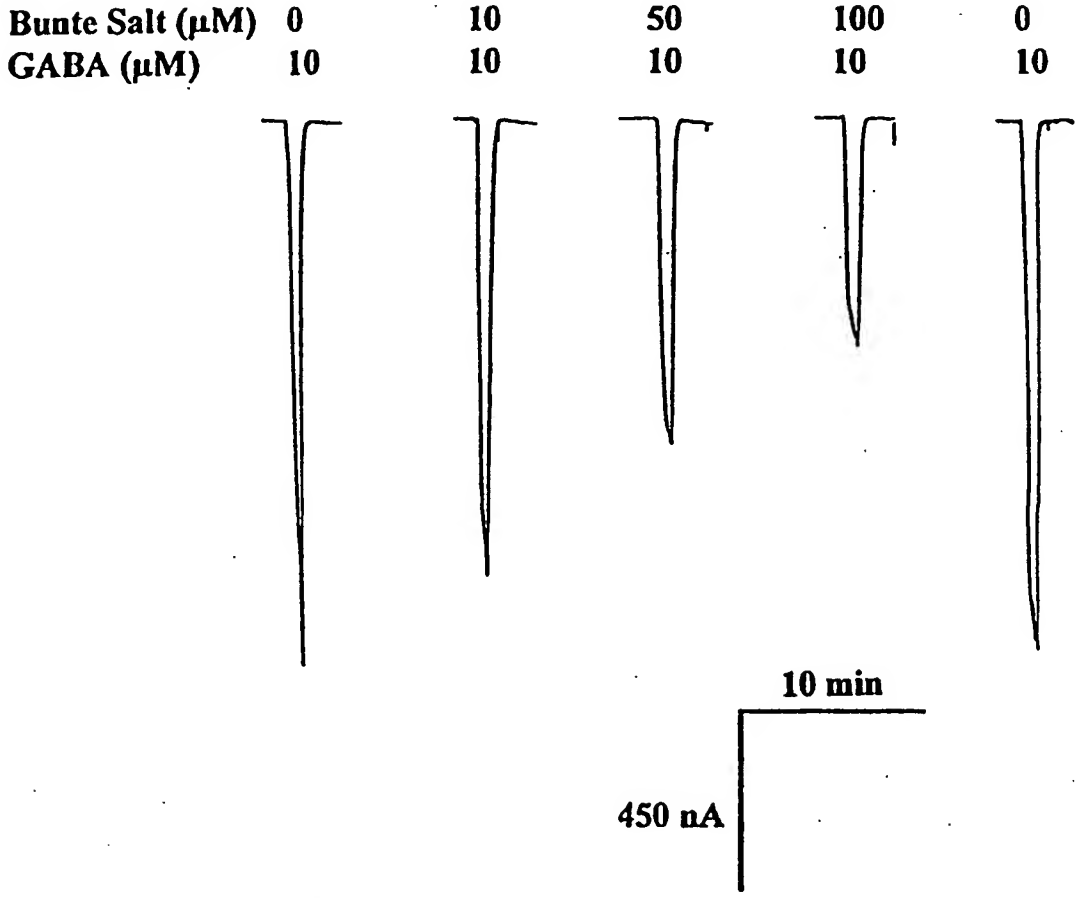
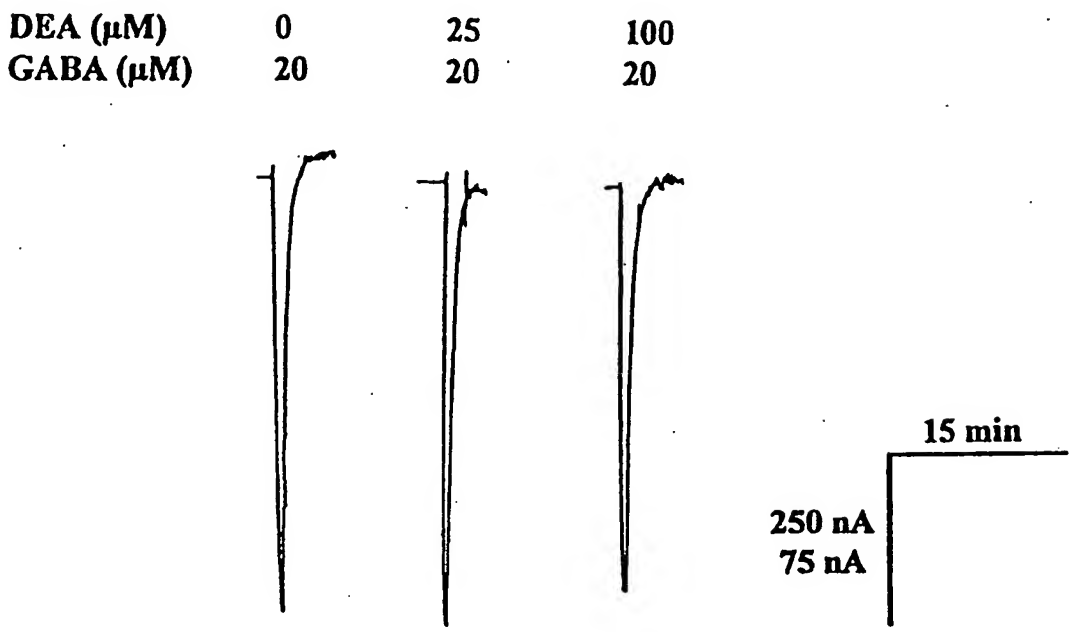


FIGURE 31


DEA (μM) 0 25 100
GABA (μM) 20 20 20
15 min
250 nA
75 nA

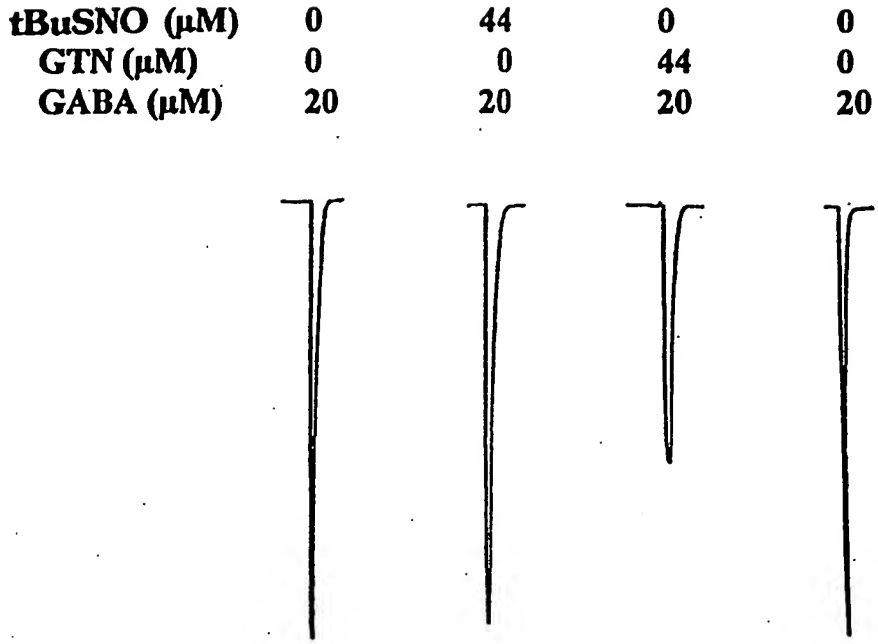
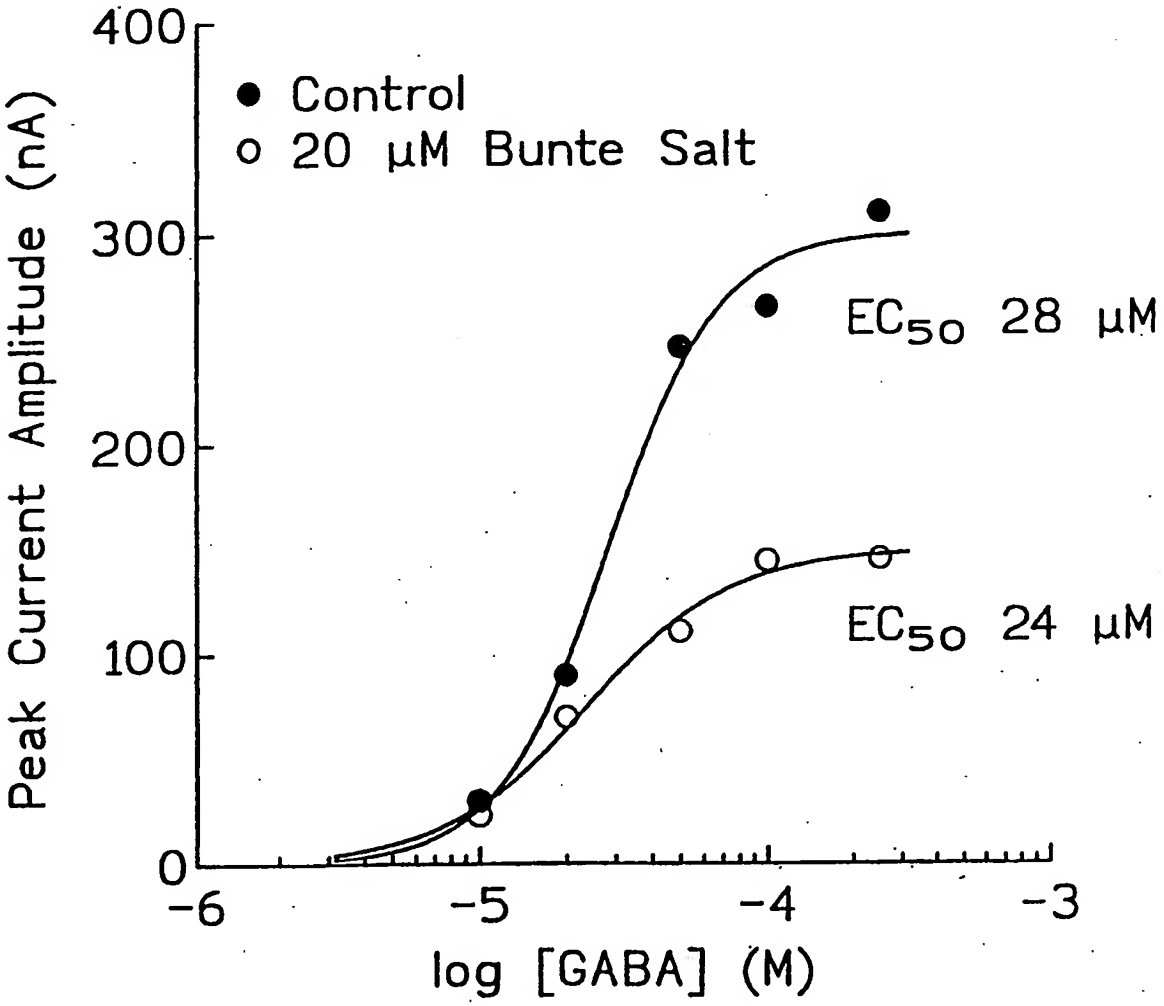

tBuSNO (μM) 0 44 0 0
GTN (μM) 0 0 44 0
GABA (μM) 20 20 20 20

FIGURE 32


400
300
200
100
0
Peak Current Amplitude (nA)
● Control
o 20 µM Bunte Salt
EC50 28 µM
EC50 24 µM
-6
-5
-4
-3
log [GABA] (M)

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 203/04, 327/34, C07D 209/28, 233/64, 495/04, C07C 211/49, C07F 9/38, C07D 295/088, 207/16, 499/32, 473/08, C07C 211/42, C07D 219/10, 307/30, 401/14, 401/12, 407/04, 417/12, C07H 15/252, A61K 31/21

A2

(11) International Publication Number: WO 00/61537

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/EP00/03234

(22) International Filing Date: 11 April 2000 (11.04.00)

(30) Priority Data:
MI99A000753 13 April 1999 (13.04.99) IT

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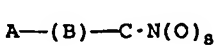
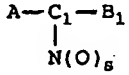
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL COMPOUNDS



(I)



(II)

(57) Abstract

Compounds or their salts having general formulas (I) and (II): wherein s is and integer equal to 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacological tests reported in the description, C and C_1 are two bivalent radicals. The precursors of the radicals B and B_1 are such as to meet the pharmacological test reported in the description.

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"PHARMACEUTICAL COMPOUNDS"

* * * * * *

The present invention relates to novel drugs for systemic use and non systemic use, and the composition thereof, to be used in oxidative stress and/or endothelial dysfuntions cases.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly . As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.
- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological

basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crasis, etc. ("Misoprostol reduces serious gastrointestinal complications in patients with

rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial." F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1998, pages 431 and 794).

The administration of anti-inflammatory drugs to patients in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can cause problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers further worsen respiratory diseases such as asthma. Therefore in asthmatic patients reduced doses of said drugs must be used in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial dysfunctions, the therapeutic action or the tolerability of

these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary cholinergic incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are charaterized by similar problems as to tolerability and/or efficacy in the mentioned pathological conditions of oxidative stress and/or endothelial

dysfuntions.

Antiallergic drugs, for example cetirizine, montelukast, etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarihtromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastro-intestinal irritability.

Antitumoral drugs, for example doxorubicine, daunorubicin, cisplatinum, etc., have high toxicity, towards different organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of

oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colinomimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

The need was felt to have available drugs showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a novel class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formulas (I) and (II):

$$A—B—C\text{-}N(O)_s \qquad (I)$$

wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

A = $R—T_1$-, wherein

R is the drug radical and

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero

or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B—X_2—T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

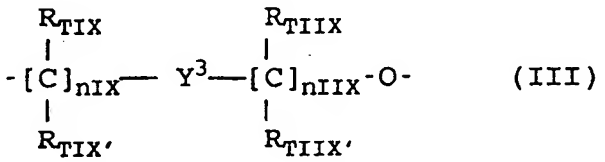
$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging bond as defined below;

C is the bivalent $-T_C-Y-$ radical, wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is an alkylenoxy group R'O wherein R' is linear or branched when possible C_1-C_{20}, preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring may have side chains of R' type, R' being as above defined; or



(III)

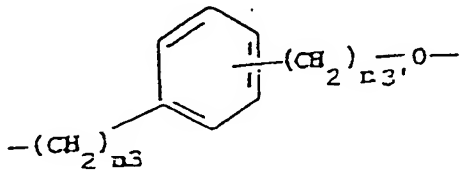
wherein:

nIX is an integer between 0 and 3, preferably 1;

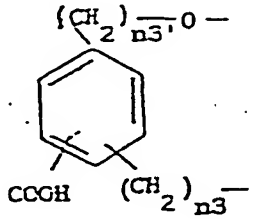
nIIX is an integer between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

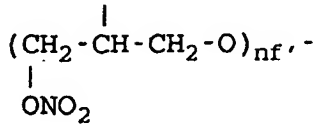
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring having 5 or 6 atoms.

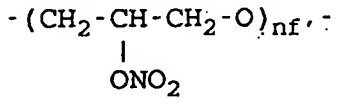


wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



wherein n3 and n3' have the above mentioned meaning

- 

- 

wherein nf' is an integer from 1 to 6 preferably from

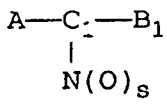
1 to 4;

- $-(CH(R_{1f})-CH_2-O)_{nf}-$

- $-(CH_2-CH(R_{1f})-O)_{nf}-$

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4;

preferably Y = -R'O- wherein R' is as above defined; preferably R' is a C_1-C_6 alkylene;



(II)

wherein:

C_1 = $-T_{CI}-Y'(-T_{CII}-)$

wherein T_{CI} and T_{CII} are equal or different;

T_{CI}= (CO) when t = 0, T_{CI} = X when t' = 0, X being as above defined;

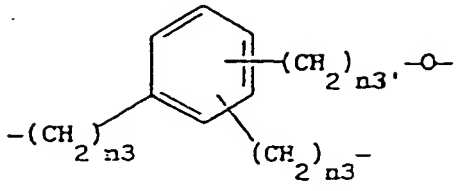
T_{CII}= $(CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that tI = 1 when tII = 0, and tI = 0 when tII = 1; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably:

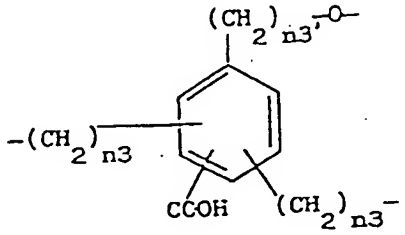
- a -R'O(-)- group wherein R' is as above defined,

preferably from 1 to 6 carbon atoms, most preferably

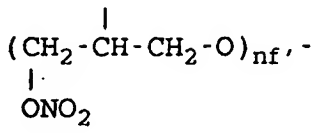
2-4, or



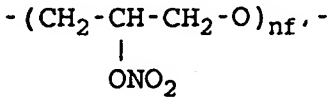
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



wherein n3 and n3' have the above mentioned meaning;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

- $-(CH-CH_2-O)_{nf}-$
  R_{1f}

  wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

- $-(CH_2-CH-O)_{nf}-$
  R_{1f}

  wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably Y' = $-R'O-$ wherein R' is a linear or branched C_2-C_4, the oxygen which in Y' is covalently linked to the $-N(O)_s$ group is at the end of the free bond indicated in C_1 formula;

B_1 = $-T_{BII}—X_{2a}$

wherein X_{2a} is a monovalent radical as defined below, T_{BII} = (CO) when tI = 0, T_{BII} = X when tII = 0, X being as above defined;

- X_2, bivalent radical, is such that the corresponding precursor of B: $-T_B—X_2—T_{BI}-$ meets the test 4, precursor in which the T_B and T_{BI} free valence are each saturated with -OZ, -Z, or with $-Z^I-N-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as defined below, depending on the fact that T_B and/or T_{BI} = CO or X, in

connection with the values of t, t', tx and txx;

- X_{2a} monovalent radical, such that the corresponding precursor of B_1 -T_{BII}—X_{2a} meets the test 4, precursor wherein the free valence of T_{BII} is saturated with -OZ, -Z or with $-Z^{I}-N(-Z^{II})-$, Z^{I} and Z^{II} being equal or different and having the Z values as defined below, depending on the fact that T_{BII} = CO or X, in connection with the values of tI and tII;
- the drug A = R—T_1-, wherein the free valence is saturated as indicated hereinafter:
  - when t' = 0 with:
    - O-Z wherein Z = H or R_{1a}, R_{1a} being a linear or when possible branched C_1-C_{10} alkyl, preferably C_1-C_5, or with
    - $-Z^{I}-N(-Z^{II})-$, Z^{I} and Z^{II} being as above defined,
  - when t = 0 with -Z, wherein Z is as above defined,

with the proviso that the drug is not a steroid, is such to meet at least one of the tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula A = R-

T_1- wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the

carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N-ω-nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrified, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison in

comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- the precursors of B or B_1 with the free valences saturated as above defined must meet test 4: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

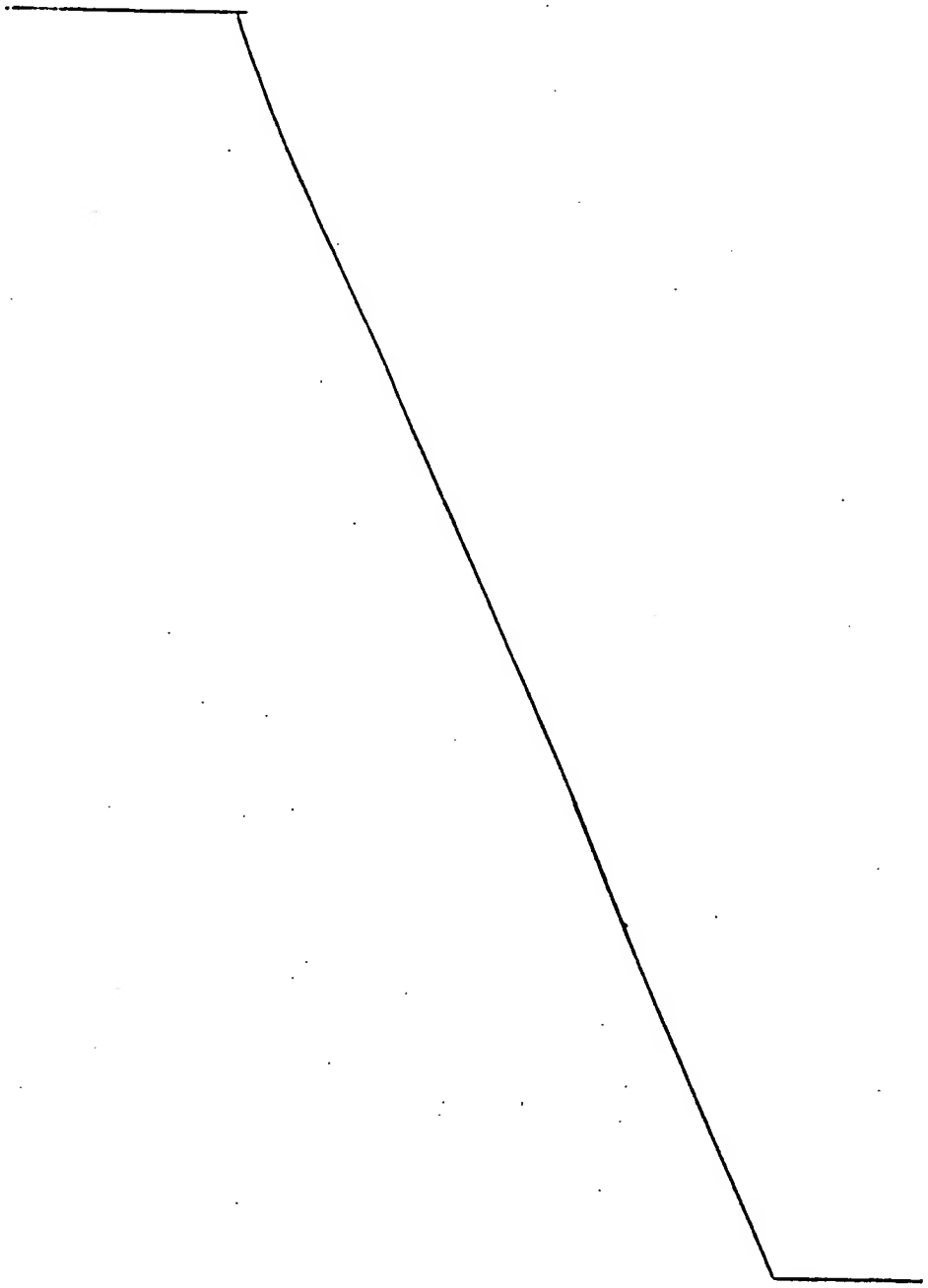
wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH;

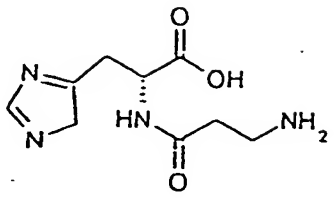
the precursor complies with test 4 when the percentage of inhibition as above defined is equal to or higher than 50%.

Preferably the precursor compound of B or B_1 (precursor of the X_2 or X_{2a} radical in the formulas (I) and (II) respectively), is selected from the following classes of compounds:

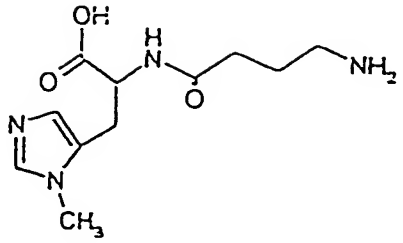
- Aminoacids, selected from the following: L-carnosine

(formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetyl-penicillamine (CVI), cysteine (CVII), N-acetyl-cysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:

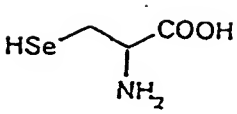




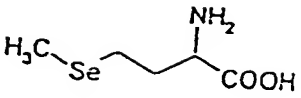
(CI)



(CII)



(CIII)



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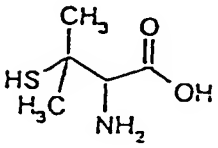
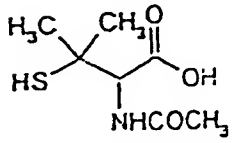
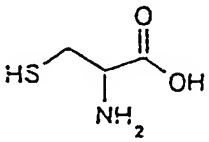


(CV)



(CVI)



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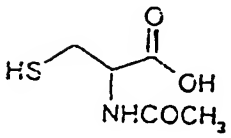

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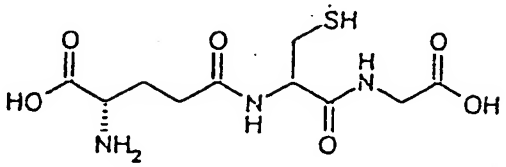
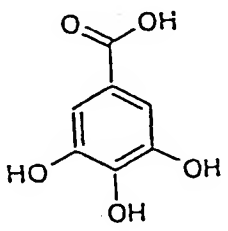


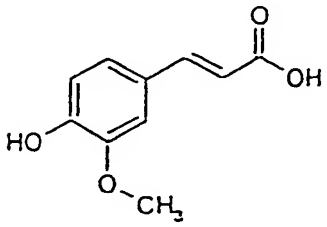
(CIX)

hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro

caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



(DI)



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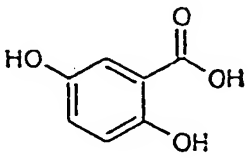

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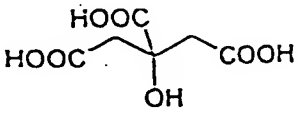
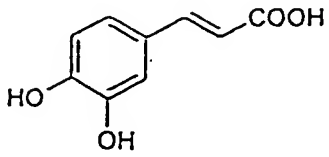
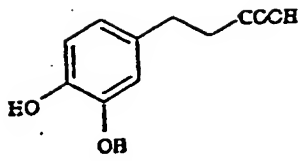


(DIV)



(DV)



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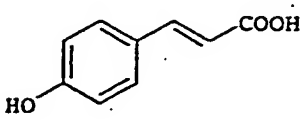
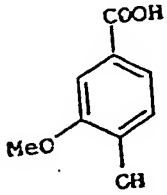


(DVII)



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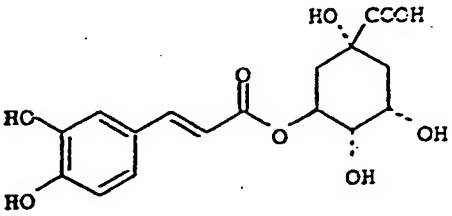
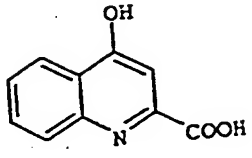
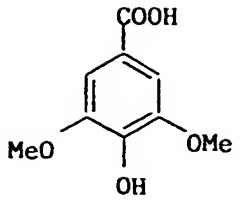


(DIX)

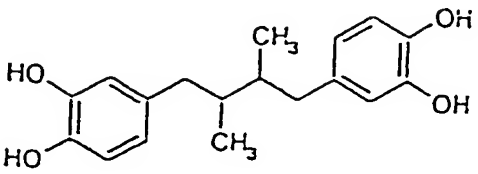


(DX)

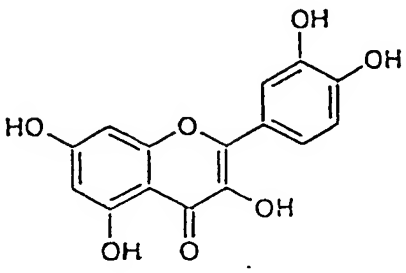


(DXI)

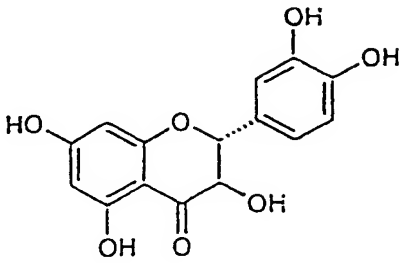
- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-ter-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-ter-butyl-p-hydroxytoluene (EXX), p-ter-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



(EI)



(EII)



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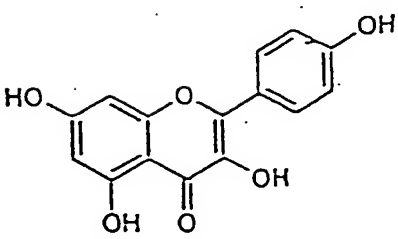
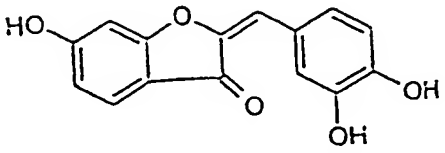
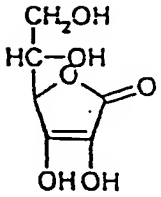


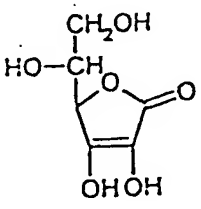
(EIV)



(EV)



(EVI)



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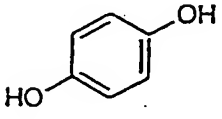

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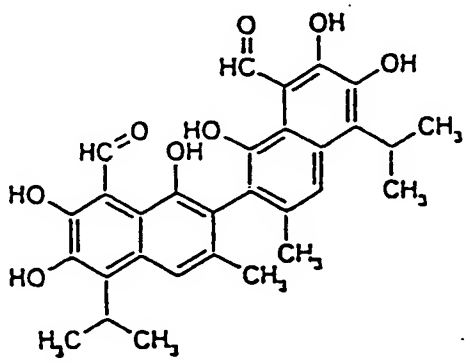

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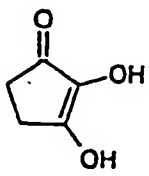

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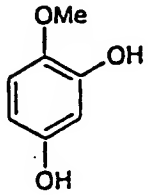

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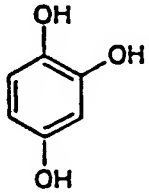

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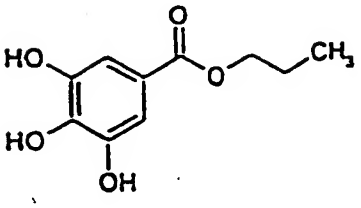

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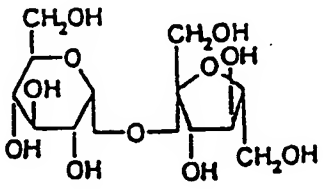

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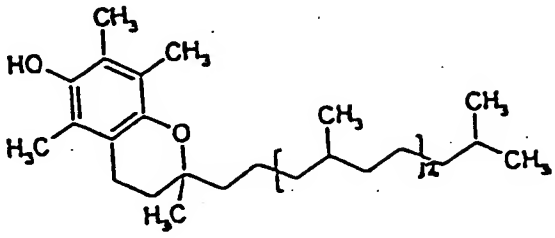

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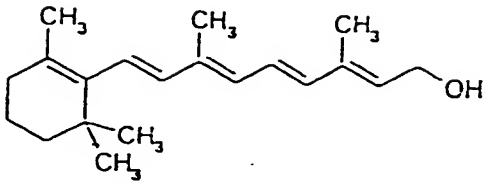
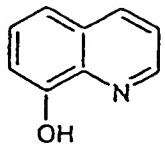


(EXVI)



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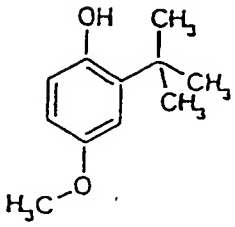
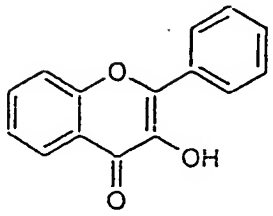


(EXVIII)



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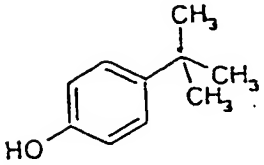
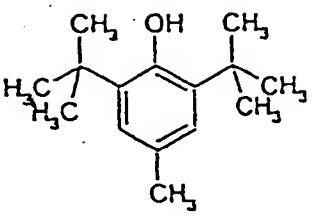
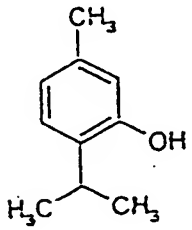


(EXXI)



(EXX)



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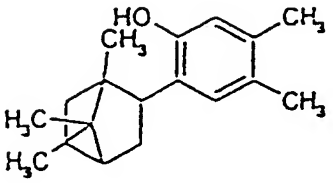

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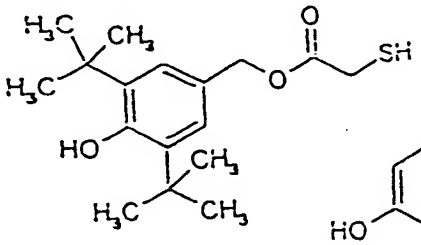

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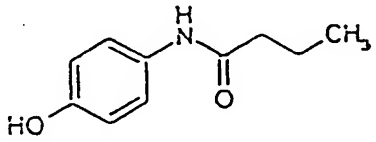

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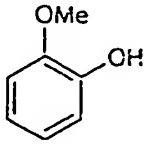

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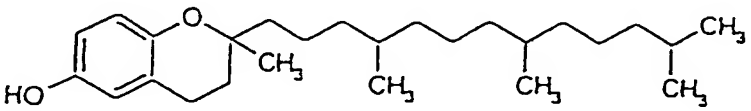

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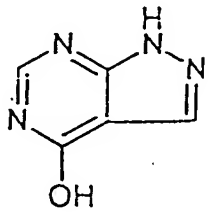
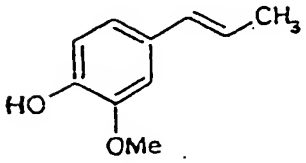


(EXXXI)



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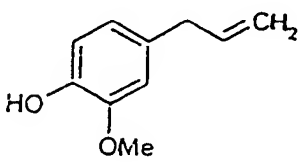

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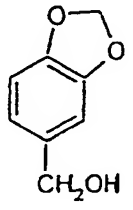
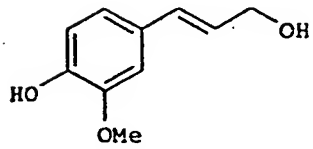


(EXXX)



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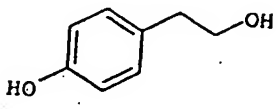

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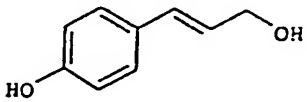

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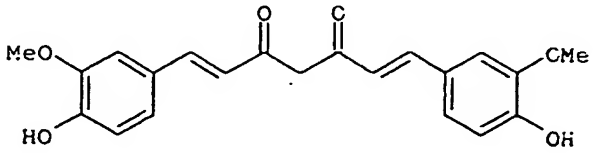
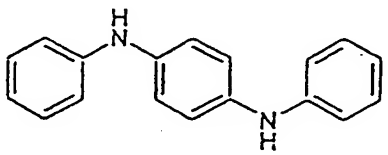
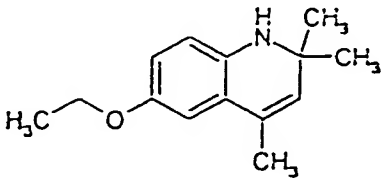


(EXXXV)

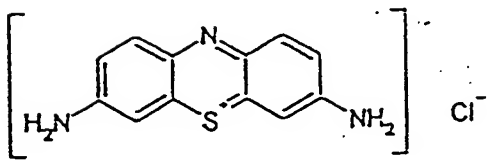
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



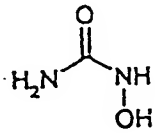
(MI)



(MII)



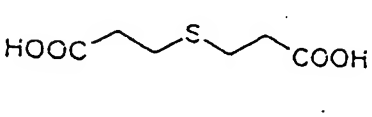
(MIII)



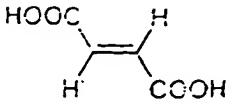
(MIV)

- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid

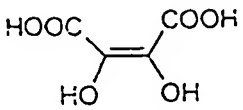
(NIII), thioctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylendioxycinnamic acid (NVI-I), piperonylic acid (NVIII):



(NI)

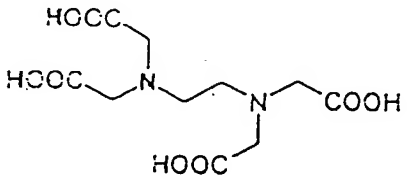


(NII)

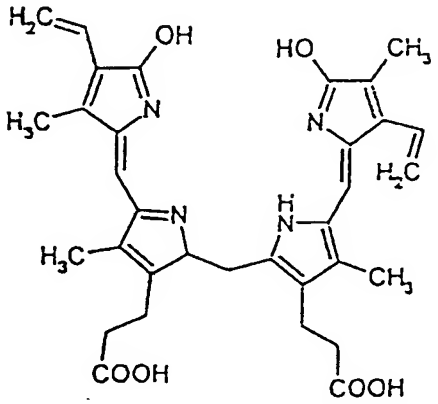


(NIII)

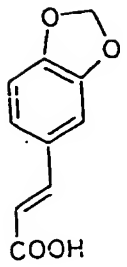
(NIV)



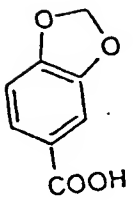
(NV)



(NVI)



(NVII)



(NVIII)

The above mentioned precursors are prepared according to the known methods in the prior art, for example described in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers and optical isomers can be used.

Tests 1-3 that are carried out for selecting the precursor drug (hereafter indicated in the tests also as "drug") to be used for the synthesis of the products of the invention are in details the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphydril reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32 1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intermuscular route),

2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (sub cutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symptoms. The animals are sacrificed after 24 hours and then one proceeds to the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I) and (II), when the group of

rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo) form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the

wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the drug at a 10^{-4}M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I) and (II), when a statistically significant inhibition of apoptosis (cellular damage) induced by CIP with respect to the group treated with CIP alone is not obtained at $p < 0.01$.

Test 3 (L-NAME): evaluation of the endothelial dysfunction

induced by administration of L-NAME (N^{w}-nitro-L-arginine-methyl ester) J. Clin. Investigation 90, 278-281,1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxy-methylcellulose, dose: 5 ml/Kg when the drug is administered by os, phisiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperiteneal, intravenous or intramuscular route. The drug is administered at that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there

is no evident toxicity in the animals, i.e a toxicity recognizable for its symptoms. The drug is administered once a day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmaco-therapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no

longer tolerated.

Test 4 is a colorimetric test which affords to establish whether the precursor of B or B_1 (precursor of the X_2 or X_{2a} of the formulas (I) and (II) respectively), inhibits the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995). 100 μM solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wave length of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound together with DPPH and of the solution containing only DPPH.

The B or B_1 precursor satisfies test 4 if their effectiveness in inhibiting radical production as above defined, is equal to or higher than 50% at the indicated concentration (10^{-4} M).

Unexpectedly the products of the invention of the formulas (I) and (II) in oxidative stress conditions have an improved therapeutic index compared with the precursor drugs.

For illustrative purposes the above mentioned tests are referred to the following compounds (see the Examples):

Test 1: precursor drug: indomethacin

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) and (II) of the present invention.

Test 2: precursor drugs: indomethacin, paracetamol and mesalamine

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) and (II) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine

according to test 2 could not be used as a precursor to prepare the compounds (I) and (II) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) and (II) of the present invention.

Test 3 (L-NAME) precursor drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

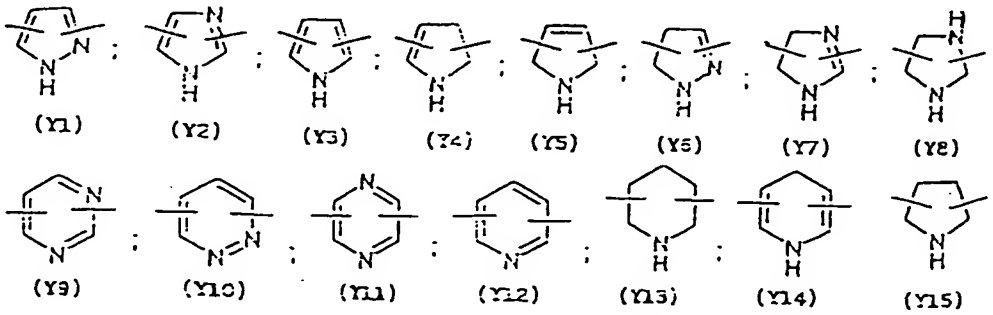
Therefore they can be used as precursors to prepare the compounds (I) and (II) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) and (II) of the present invention.

Test 4 (test for the precursor of B and B_1 used as bivalent linking bridge): precursor N-acetylcysteine

N-acetylcysteine inhibits of 100% the production of radicals induced by DPPH, therefore it meets test 4. Therefore it can be used as precursor of B or B_1.

In formula (III) Y^3 is preferably selected from the following:



The most preferred of Y^3 is Y12 (pyridyl) substituted in positions 2 and 6. The bonds can also be in asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The compounds according to the present invention of formula (I) and (II) can be transformed into the corresponding salts. For example one route to form the salts is the following: when in the molecule one nitrogen atom sufficiently basic to be salified, in organic solvent such as for example acetonitrile, tetrahydrofuran, is present, it is reacted with an equimolecular amount of the corresponding organic or inorganic acid. To form the salt, preferably in the formula of the invention compounds Y or Y' of formula (III) is present.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in the therapeutic indications of the precursor drug, allowing to obtain the advantages exemplified hereinafter for some groups

of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and is under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of α- or β-blocker type: the action spectrum of the compounds of formula (I) and (II) results wider than that of the starting drugs; to a direct action on the smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic vessels is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.
- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.
- Diphosphonates: the toxicity relating to the gastrointe-

stinal tract is drastically lowered.

- Phosphodiesterase (PDE) (bronchodilators) inhibitors: the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and hypoglycaemizing) antibiotic, antiviral, antitumoral, anticolitic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in formulas (I) and (II) of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen,

cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyrocetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibu-

fenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit;

for respiratory and urogenital apparatus drugs (bronchodilators and drugs active on the cholinergic system, expectorants/mucolytics, antiasthmatic/antiallergic antihistaminic drugs), the following can be mentioned:

broncodilators and drugs active on the cholinergic system : acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domiodol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, leto-

steine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

for cardiovascular drugs (ACE-inhibitors, beta-blockers, antithrombotic and vasodilator drugs, antidiabetic and hypoglycemic drugs), the following can be mentioned:

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsa-

licylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

for antitumor drugs, the following can be mentioned: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer

sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

for antiulcer drugs the following can be mentioned: ε-acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

among anti-hyperlipidemic drugs (statines) the following can be mentioned: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium, simvastatin;

among antibiotic/antiviral drugs the following can be mentioned:

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin,

cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycin, propcillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandromycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin,

paromomycin, ribostamycin, sisomicin, spectinomycin, streptomicin, tobramycin, trospectomycin;

bacampicillin, cefcapene pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine; p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline, Acediasulfone, dapsone, succisulfone, p-sulfanilylbenzylamine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole,

sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, scrivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

among inhibitors of the bone resorption (diphosphonates) the following can be mentioned: alendronic acid, butedronic acid, etidronic acid, oxidronic acid, pamidronic acid, risedronic acid;

among antidemence drugs the following can be mentioned: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

The preferred substances are the following:

among anti-inflammatories: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen,

ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

among analgesic drugs: acetaminophen, acetylsalicylsalicylic acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacereine, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

among respiratory and urogenital apparatus drugs: (bronchodilators, drugs active on the cholinergic system, expectorants / mucolytics, antiasthmatics/antiallergic antihistaminic drugs):

bronchodilators and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, difhylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetrahydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaiacol, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

among cardiovascular drugs:

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

Beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

among antitumor drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

among antiulcer drugs: cimetidine, omeprazole, pantoprazole;

among antihyperlipidemic drugs: lovastatin, pravastatin sodium, simvastatin;

among antibiotic/antiviral drugs:

antibiotic drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid,

apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

among inhibitors of the bone reabsorption: alendronic acid, etidronic acid, pamidronic acid;

among antidemence drugs: oxiracetam, tacrine, velnacrine.

The above mentioned substances, precursor drugs, are prepared according to the methods known in the prior art. See for example in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers, comprising optical isomers, can be used.

Tomoxiprol is obtained according to the method describeid in EP 12,866.

The compounds of formula (I) or (II) are prepared with synthesis methods mentioned below.

The choice of the reactions for each method depends on the reactive groups present in the precursor drug molecule, in the precursor compound of B or B_1, which can be, as above mentioned, bivalent or monovalent, and in the precursor compound of C.

The reactions are carried out with methods well known in the prior art, which allow to obtain bonds among the precursor

drug, the precursor drug of B or B_1 and the precursor compound of C as above defined.

When the reactive function of the precursor drug (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function can be restored with the methods well known in the prior art.

Some synthesis schemes for obtaining the compounds of the invention are reported hereinafter:

A) Synthesis of the compounds of formula (I).

1. Synthesis of the compound obtained by reaction between the precursor drug and the compound precursor of B.

1a. When the drug has general formula R-COOH and the functional group of the precursor compound of B which binds itself to the drug carboxylic function has the formula XZ, X being as above defined and Z = H, the reactions which take place depend on the nature of the second reactive group present in the precursor compound of B.

1a.1 When the second reactive group present in the precursor compound of B is a carboxylic group, the synthesis general scheme expects the initial formation of the halide of the R-COHal acid (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:

$$RCOOH \dashrightarrow RCOHal + H\text{-}X\text{-}X_2\text{-}COOH \dashrightarrow$$

$$R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COOH \qquad (IA.1)$$

X_2, T_1, T_B being as above defined.

When in the two reaction compounds other functional groups COOH and/or HX are present, they must be protected before the reaction according to the methods known in the art; for example as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The RCOHal acylhalide is prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, P^{III} or P^{V} halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

Specifically, if the HX group of the precursor compound of B is NH_2, or OH or SH, the precursor drug of formula R-COOH is first converted into the corresponding acyl halide RCOHal, as above mentioned, and then reacted with the HX group of the precursor compound of B in the presence of an organic base, such as triethylamine, pyridine, etc. using an inert solvent in the reaction conditions such as toluene, tetrahydrofuran, etc. at a temperature in the range 0°C-25°C.

Alternatively to the previous synthesis, the precursor drug of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide in solvent such as for example DMF, THF, chlo-

roform etc. at a temperature in the range -5°C-50°C and the obtained commpound reacted in situ with the reactive function of the precursor compound of B for obtaining the compound of formula (IA.1).

1a.2 When the precursor compound of B contains two functional groups XZ, equal to or different from each other, X being as above defined and Z = H, the precursor drug having formula R-COOH is first treated with an agent activating the carboxyl group, as above described in 1a.1, and then with the precursor compound of B, after having protected one of the two reactive HX groups, for example with acetyl or ter-butyloxycarbonyl, restoring the initial function at the synthesis end. The scheme is the following:

$$RCOOH \xrightarrow{CDI,\ HX\text{-}X_2\text{-}X\text{-}G} R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}X\text{-}G \dashrightarrow R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}XH \quad (IA.2)$$

wherein X, T_1, T_B, X_2 are as above defined and G is a protective group of the HX function.

2. Nitroxyderivative synthesis.

2a.1 When the compound obtained at the end of the previous step 1a. has formula (IA.1), the acid can be converted into the corresponding sodic salt and then one can follow the known prior art methods for preparing the final compound, for example according to one of the following synthesis schemes:

A.) $R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COONa + R_4\text{-}X_1\text{-}R_3 \dashrightarrow$

$$R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3 \quad (1A.1b) \xrightarrow{AgNO_3} R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$$

wherein T_1, T_B, X_2, T_{BI}, T_C are as above defined, R_4 is selected from Cl, Br, Y is as above defined, X_1 is the Y radical free from the oxygen atom, R_3 is Cl, Br, Iodine, OH. If R_3 = OH the compound of formula (1A.1b) is subjected to halogenation, for example with PBr_3, PCl_5, $SOCl_2$, $PPh_3 + I_2$, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran. If R_3 is Cl, Br, Iodine, the compound of formula (1A.1b) is directly reacted with $AgNO_3$ as above mentioned.

B.) $R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COONa + Hal\text{-}Y\text{-}NO_2 \dashrightarrow R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$

C.)

$$R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COCl + R_5\text{-}X_1\text{-}R_3 \rightarrow R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3 \quad (1A.1c)$$

$$R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3 \xrightarrow{AgNO_3} R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$$

wherein R_5 = OH or NHR_{1C}, R_{1C}, R_3 and the other symbols being as above defined.

The above shown reactions are well known in the prior art. See for example the patent applications in the name of the Applicant WO 94/12463, WO 95/09831 and WO 95/30641.

When X_1 is a linear C_4 alkyl, the corresponding acid $R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COOH$ is reacted with triphenylphosphine in the

presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran obtaining the compound (1A.1c) wherein R_3 = Br.

2a.2 When the compound obtained at the end of th previous step 1a has formula (IA.2), the corresponding nitroxyderivative is obtained by treating an halogen-carboxylic acid of formula Hal-X_1-COOH, X_1 being as above defined, first with an agent activating the carboxyl group as described in 1A.1, and then with the compound of formula (IA.2), obtaining an halogen derivative, which is isolated and then dissolved in organic solvent, (ref. paragraph 2a.1), and treated with silver nitrate. The global reaction scheme is the following:

$$\text{Hal-}X_1\text{-COOH} \xrightarrow{\text{1) CDI, 2) R-}T_1\text{-}T_B\text{-}X_2\text{-XH}} \text{R-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-Hal} \xrightarrow{AgNO_3} \text{R-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-Y-}NO_2$$

wherein T_1, T_B, X_2, T_{BI}, T_C, Y are as above defined.

Alternatively, the halide Hal-X_1-COCl can be used, wherein Hal is preferably bromine, which is let react with the compound of formula (IA.2).

1b. When the drug precursor has the reactive function HX, wherein X is as above defined, instead of a carboxylic group, the two functional groups present on the precursor compound of B can be the following:

1b.1 A carboxylic group, which reacts with the HX function of the drug precursor, and a HX group, the latter reactive group of the precursor compound of B being equal to or different from the functional group of the drug precursor. The formula of the precursor compound of B is of the H-X-X_2-COOH type, wherein X and X_2 are as above defined. The H-X- function of the precursor compound of B is protected according to the known prior art methods and the carboxyl group is reacted, as above mentioned, according to the following scheme:

H-X-X_2-COOH ----→ G-X-X_2-COOH + R-XH ---→

R-T_1-T_B-X_2-X-G -----→ R-T_1-T_B-X_2-X-H (1B.1)

At the end of the reaction the HX function of the precursor compound of B is restored.

1b.2 When the precursor compound of B contains two carboxylic groups, it is treated with an equimolar amount of an agent activating the carboxyl group under the conditions previously described in 1a.1, and then reacted with the reactive HX function of the drug precursor molecule. Possible other reactive functions of HX type present in the two compounds must be protected as previously mentioned. Lastly a compound of formula R-T_1-T_B-X_2-COOH (1B.2) is obtained.

2b. Nitroxyderivative synthesis.

2b.1 To obtain the final nitroxyderivative starting from the

compound of formula R-T_--T_B-X_2-X-H (1B.1), obtained at the end of the synthesis described in 1b.1, the (1B.1) compound is reacted with an halogenacid of formula Hal-X_1-COOH which has been treated as previously described in paragraph 1a.1, or with the corresponding halogenacid chloride. The resulting compound is dissolved in organic solvent, for example acetonitrile or tetrahydrofuran and reacted with silver nitrate.

2b.2 To obtain the final nitroxyderivative starting from the compound of formula R-T_--T_B-X_2-COOH (1B.2), obtained at the end of the synthesis described in 1b.2, the acid is transformed into the corresponding sodic salt, it is reacted with a R_4-X_1-R_3 compound, previously defined in the reaction A. scheme of paragraph 2a.1, obtaining according to the same process therein mentioned the final nitroxyderivative. Alternatively, when X_1 is a linear C_4 alkyl, the acid (1B.2) is reacted with triphenyl-phosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran and the resulting compound dissolved in organic solvent for example acetonitrile, tetrahydrofuran, is reacted with silver nitrate.

2b.3 Alternatively to the synthesis process according to 1b.1 and 2b.1, it is possible to react in a first step the HX-function of the precursor compound of B HX-X_2-COOH with

the acyl chloride of an halogenacid of formula Hal-X_1-CO-Cl, wherein Hal is preferably Br, and subsequently the carboxylic function of the so obtained compound, with the drug precursor R-HX. In the third and last step the -Hal group is substituted with $-ONO_2$ according to the process described in 2b.1. The reaction scheme is the following:

$$HX\text{-}X_2\text{-}COOH + Hal\text{-}X_1\text{-}COCl \dashrightarrow Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}COOH$$

$$Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}COOH \quad (2B.3) \xrightarrow{R\text{-}XH} Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}T_1\text{-}R$$

$$Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}T_1\text{-}R \xrightarrow{AgNO_3} O_2N\text{-}Y\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}T_1\text{-}R$$

wherein T_C, T_{BI}, T_B, T_1, X_2, X_1, Y are as above defined. In the previous scheme the nitration can alternatively be carried out on the acid compound of formula (2B.3).

B) Synthesis of compounds of formula (II).

1a. When the drug precursor is of formula R-COOH and the precursor compound of B_1 contains only one functional reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corresponding acyl-halide, or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an halogen-acid compound, said function being equal to or different from that present on the precursor compound of B_1, said halogen-acid having the formula:

$$\begin{array}{l} HX\text{-}X_1'\text{-}COOH \\ \quad | \\ \quad Hal \end{array} \qquad (IIA.1)$$

wherein X_1' is Y' as above defined without the oxygen atom

through which the $-NO_2$ group is linked, X and Hal are as above defined.

The compound (IIA.1) can be obtained with the known method of the prior art. For example when X = NH, it can be obtained from the corresponding hydroxy-aminoacid, protecting the aminic group by the corresponding ter-butyloxycarbonyl derivative and transforming the hydroxyl function into halogen group as described for the halogenation of the compound (1A.1b) in 2a.1. The free carboxylic function of the compound resulting from the reaction with the molecule of the drug precursor is reacted with the function present in the molecule of the precursor compound of B_1, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the halogen atom (Hal) present on the radical X'_1 is substituted with an ONO_2 group by adding $AgNO_3$ to an organic solution of the compound. The reaction scheme is the following, exemplified starting from the RCOCl acid halide:

$$R\text{-}COCl + HX\text{-}X_1'\text{-}COOH \rightarrow R\text{-}T_1\text{-}T_{CI}\text{-}X_1'\text{-}COOH \ (IIA.2) + HX\text{-}X_{2a} \rightarrow$$

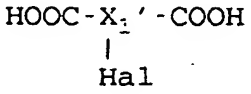
(Hal on X_1'; Hal on X_1')

$$R\text{-}T_1\text{-}T_{CI}\text{-}X_1'\text{-}T_{CII}\text{-}T_{BII}\text{-}X_{2a} + AgNO_3 \rightarrow R\text{-}T_1\text{-}T_{CI}\text{-}X_1'\text{-}T_{BII}\text{-}X_{2a}$$

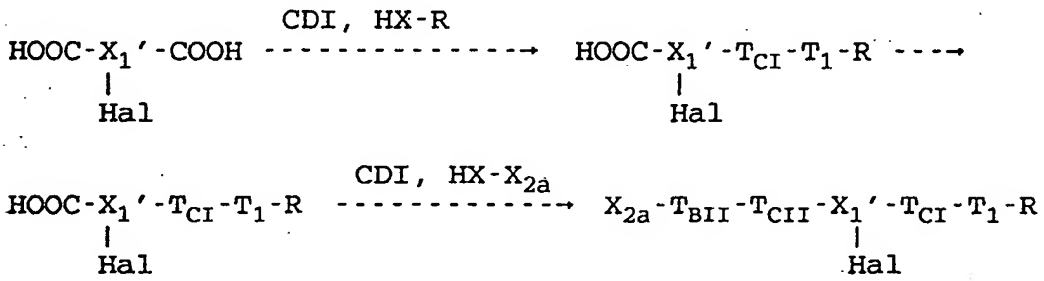
(Hal on X_1'; ONO_2 on X_1')

1b. When the drug precursor and the precursor compound of B_1 contain each a reactive group of general formula XH, the

two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an halogenacid compound of formula



X_1' being as above defined, said compound being prepared from the corresponding hydroxy-diacid as described for the halogenation of the compound (1A.1b) in 2a.1. The halogendiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the drug precursor molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first, and reacted with the precursor compound of B_1 according to the following scheme:



The halogen atom is then substituted with the ONO_2 group as above mentioned.

3. Synthesis of the nitroso (s=1) derivatives of formula (I).

3a.1 The compound of formula (1A.1b) wherein R_3 = OH is reacted with sodium nitrite in a solvent formed of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is widely illustrated in the prior art. The general scheme is the following:

$R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}OH + NaNO_2 \dashrightarrow A\text{-}B\text{-}C\text{-}NO$

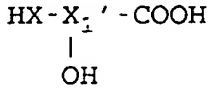
3a.2 If the compound obtained at the end of step A in 1a.2 has formula (IA.2) the corresponding nitroso derivative is obtained treating an hydroxyacid of formula $HO\text{-}X_1\text{-}COOH$, X_1 being as above defined, first with an agent activating the carboxyl group, as described in 1a.1, then reacting it with 1A.2 and the resulting product with sodium nitrite as described in 3a.1.

3b.1 To obtain the nitroso derivative starting from the compound of formula $R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}XH$ (1B.1) obtained at the end of the synthesis described in 1b.1, the compound (1B.1) is reacted with an hydroxyacid as described in 3a.2.

3b.2 To obtain the nitroso derivative from the compound of formula $R\text{-}T_1\text{-}T_B\text{-}X_2\text{-}COOH$ (1B.2) obtained at the end of the synthesis described in 1b.2, the acid is transformed into the sodic salt and reacted with a compound $Hal\text{-}X_1\text{-}OH$, as previously described, and the obtained alcohol is treated as described in 3a.1.

4) Synthesis of the nitroso derivatives of formula (II)

4a.1 When the drug is of formula R-COOH and the precursor compound of B_1 contains only one function reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corrsponding acyl-halide or treated with an agent activating the carboxyl group as describied in 1a.1, and then reacted with the HX function of an hydroxy-acid compound, said function being equal to or different from that present on the precursor compound of B_1, said hydroxy-acid having the formula:

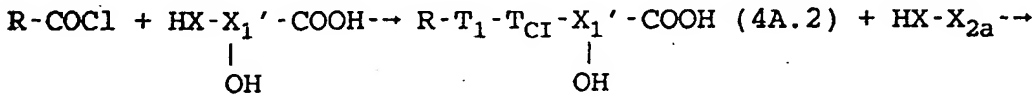


(4A.1)

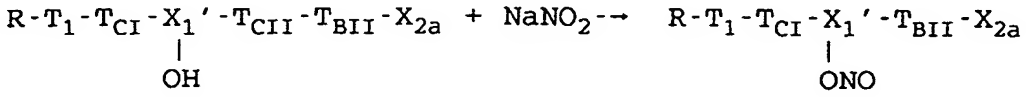
wherein X_1' is Y' as above defined without the oxygen atom through which the -NO group is linked, X is as above defined.

The free carboxylic function of the compound resulting from the reaction with the drug molecule is reacted with the function present in the molecule of the precursor compound of B_1, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the alcohol is transformed into the nitroso-derivative as described in 3a.1.

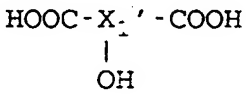
The reaction scheme is the following, exemplified starting from the RCOCl acid halide:



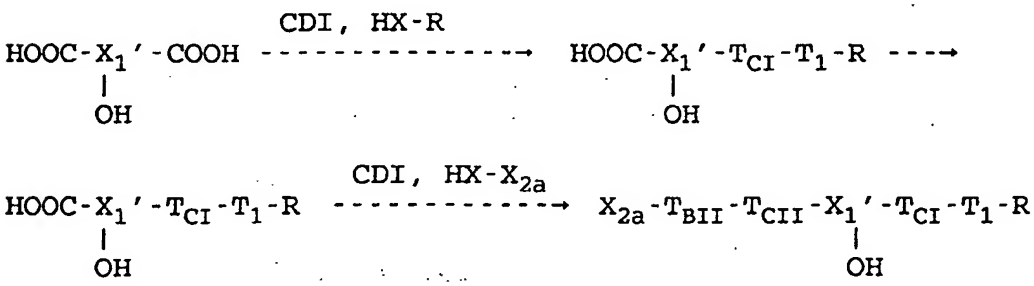
(4A.2)



4b. When the drug and the precursor compound of B_1 contain each a reactive group of general formula XH, the two groups in each of the two molecules being equal to or different from each other, wherein X is as above defined, the synthesis is carried out starting from an hydroxy-diacid compound of formula



X_1' being as above defined, said hydroxydiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the drug molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first one, and reacted with the precursor compound of B_1 according to the following scheme:



The obtained compound is reacted as described in 3a.1.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

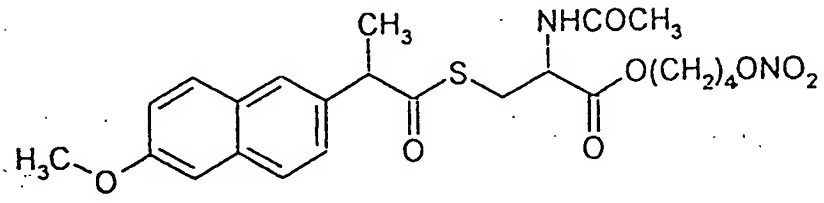
The amount on molar basis of the active principle in these formulations is the same; or lower, in comparison with that used of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

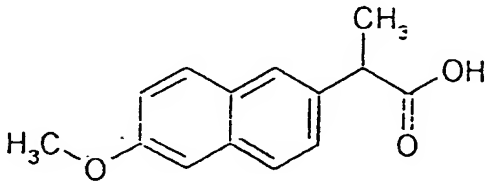
EXAMPLE 1

Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalen acetyl)cisteine 4-(nitroxy)butyl ester (NCX 2101) having formula

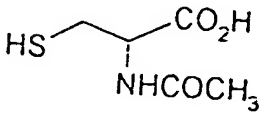


(NCX 2101)

The precursor is naproxene (Formula VI), the precursor of B is N-acetylcisteine (formula CVIII)



(VI)



(CVIII)

a) Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalen acetyl)cisteine

To a solution of 6-methoxy-α-methyl-2-naphthalenacetic acid (10 g, 43.4 mmoles) in chloroform (100 ml) and N,N-dimethylformamide (6 ml), 1,1'-carbonyldiimidazole (CDI) (7.04 g, 43.4 mmoles) is added. After 15 minutes the obtained solution is treated with (S)-N-acetylcisteine (7.08 g, 43.4 mmoles) and left at room temperature for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydrified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 11.66 g of the expected product in the form of a white solid m.p. 122°-126°C, is obtained.

^{1}H-NMR ($CDCl_3$): 7.71-7.65 (3H, m), 7.34 (1H, dd), 7.16-7.09 (2H, m), 6.36 (1H, d), 4.67 (1H, m), 4.00 (1H, q), 3.90 (3H, s) 3.32 (2H, t), 1.84 (3H, s), 1.59 (3H, d).

b) Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-napht-

halen acetyl)cisteine 4-(bromobutyl) ester

To a solution of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalenacetyl)cisteine (11.3 g, 30.1 mmoles) in tetrahydrofuran (200 ml), triphenylphosphine (23.7 g, 90.3 mmoles) and carbon tetrabromide (28.85 g, 90.3 mmoles) are added. The reaction mixture is left under stirring for 24 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 4 g of the ester in the form of a white solid with m.p. 67°-71°C, are obtained.

c) Synthesis of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalen acetyl)cisteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (1 g, 1.96 mmoles) in acetonitrile (20 ml), silver nitrate (0.66 g, 3.92 mmoles) is added. The reaction mixture is heated for 7 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 0.47 g of (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalenacetyl)cisteine 4-(nitroxy)butyl ester in the form of a white solid m.p. 56-59°C, are obtained.

^{1}H-NMR ($CDCl_3$): 7.80-7.68 (3H, m), 7.37(1H, d), 7.20-7.13 (2H, m), 6.12 (1H, d) 4.40 (2H, dd), 4.26 (1H, m), 4.15-3.87 (3H,

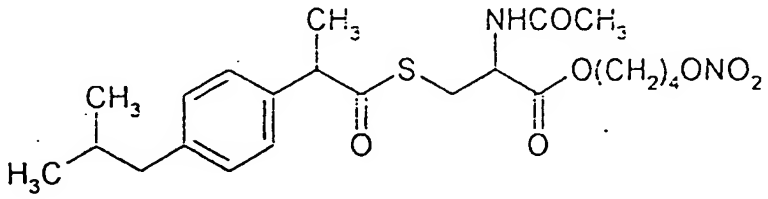
m), 3.92 (3H, s), 3.33 (2H, d), 1.86 (3H, d), 1.74-1.67 (4H, m), 1.61 (3H, d).

Elementary analysis:

Calculated	C: 56.08%	H: 5.73%	N: 5.71%	S: 6.51%
Found	C: 55.99%	H: 5.68%	N: 5.60%	S: 6.35%

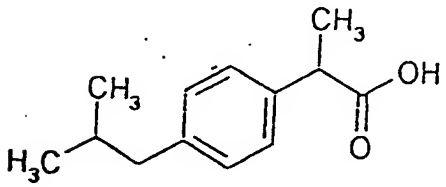
EXAMPLE 2

Synthesis of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl) benzene] acetyl)cisteine 4-(nitroxy)butyl ester (NCX 2111) having formula

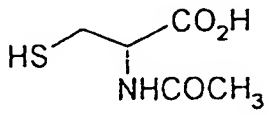


(NCX 2111)

The precursor is ibuprofen (Formula VII), the precursor of B is N-acetylcisteine (formula CVIII)



(VII)



(CVIII)

a) Synthesis of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl) benzene]acetyl)cisteine

To a solution of α-methyl[4-(2-methylpropyl)benzene] acetic acid (10 g, 48.48 mmoles) in chloroform (100 ml) and N,N-dimethylformamide (6 ml) 1,1'-carbonyldiimidazole (7.86 g,

48.48 mmoles) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcisteine (7.91 g, 48.47 mmoles) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydrified with sodium sulphate and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 13.3 g of the expected product in the form of an oil are obtained.

^{1}H-NMR ($CDCl_3$): 10.17 (1H, s) 7.13 (2H, d) 6.54 (1H, d), 4.76 (1H, m), 3.93 (1H, q), 3.42-3.30 (2H, m), 2.49 (2H, d), 1.85-1.83 (4H, m), 1.55 (3H, d), 0.93 (6H, d).

b) Syntheis of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl)-benzene]acetyl}cisteine 4-(bromobutyl) ester

To a solution of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl)benzene]acetyl}cisteine (12.8 g, 36.4 mmoles) in tetrahydrofuran (100 ml), triphenylphosphine (28.65 g, 109.23 mmoles) and carbon tetrabromide (36.23 g, 109.23 mmoles) are added. The reaction mixture is let under stirring for 48 hours at room temperature. The solvent is removed by evaporation at reduced pressure. The crude product is purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate 1/1. 5.79 g of the ester in the form of an oil are obtained.

c) Synthesis of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl)

benzene]acetyl}cisteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (5.5 g, 11.3 mmoles) in acetonitrile (100 ml) silver nitrate (2.69 g, 15.8 mmoles) is added. The reaction - mixture is heated for 24 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chomatography on silica gel eluting with cyclohexane/ethyl acetate 7/3. 1.18 g of (S)-N-acetyl-S-{α-methyl[4-(2-methylpropyl)benzene] acetyl}cisteine 4-(nitroxy)butyl ester in the form of an oil are obtained.

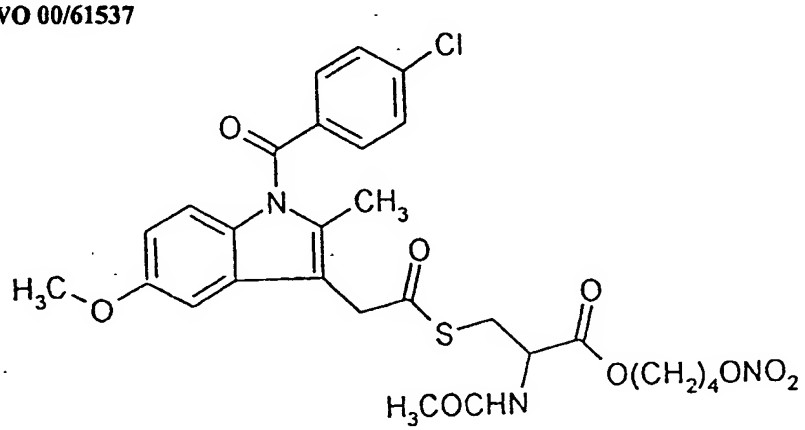
^{1}H-NMR ($CDCl_3$): 7.27-7.09 (4H, m), 6.19 (1H, d), 4.75 (1H, m), 4.47 (2H, t), 4.15-4.02 (2H, m), 3.86 (1H, q), 3.31 (2H, d), 2.44 (2H, d), 1.89 (3H, d), 1.86-1.76 (5H, m), 1.51 (3H, d), 0.89 (6H, d).

Elementary analysis:

Calculated	C: 56.39%	H: 6.88%	N: 6.00%	S: 6.84%
Found	C: 56.22%	H: 6.79%	N: 5.88%	S: 6.92%

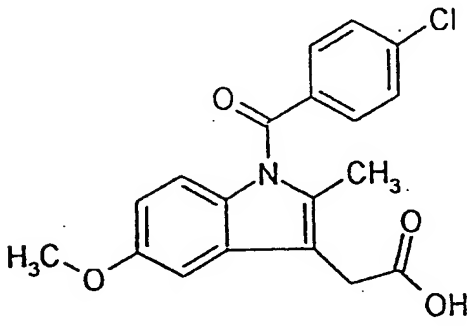
EXAMPLE 3

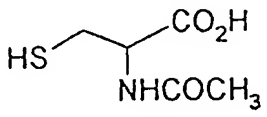
Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine 4-(nitroxy)butyl ester (NCX 2121) having formula



(NCX 2121)

The precursor is indomethacin (Formula VIII), the precursor of B is N-acetylcisteine (formula CVIII)





(VIII) (CVIII)

a) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine

To a solution of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid (10 g, 28.00 mmoles) in chloroform (100 ml) and N,N-dimethylformamide (2 ml) 1,1'-carbonyldiimidazole (4.53 g, 28.00 mmoles) is added. After 1 hour the obtained solution is treated with (S)-N-acetylcisteine (4.56 g, 28.00 mmoles) and left at room temperature for 24 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydrified with sodium sulphate

and then evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with ethyl acetate. 7.79 g of the expected product in the form of a yellow solid m.p. 129°C, are obtained.

^{1}H-NMR (DMSO-d_6): 12.90 (1H, s), 8.21 (1H, d), 7.69-7.64 (4H, m), 7.06 (1H, d), 6.96 (1H, d), 6.73 (1H, dd), 4.33 (1H, m), 4.02 (2H, s), 3.77 (3H, s), 3.33-2.96 (2H, m), 2.22 (3H, s), 1.78 (3H, s).

b) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine 4-(bromobutyl) ester

To a solution of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine (3.09 g, 6.14 mmoles) in N,N dimethylformamide (50 ml), sodium ethylate (0.42 g, 6.14 mmoles) and, after 30 minutes, 1,4-dibromobutane (2.18 ml, 18,00 mmoles) dissolved in 25 ml of N, N dimethylformamide, are added. The reaction mixture is left under stirring for 20 hours at room temperature, then it is diluted with ethyl ether and washed with water. After the organic phase has been anhydrified with sodium sulphate, the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel, eluting with cyclohexane/ethyl acetate 1/1. 1.7 g of the ester in the form of a yellow solid with m.p. 130°-134°C are obtained.

c) Synthesis of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine 4-(nitroxy)butyl ester

To a solution of the ester obtained at the end of the previous step (1.6 g, 2.5 mmoles) in acetonitrile (30 ml) silver nitrate (0.6 g, 3.51 mmoles) is added. The reaction mixture is heated for 8 hours under reflux away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate 4/6. 1.2 g of (S)-N-acetyl-S-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetyl]cisteine 4-(nitroxy)butyl ester in the form of an oil are obtained.

^{1}H-NMR ($CDCl_3$): 7.66 (2H, d), 7.48 (2H, d), 6.90 (2H, m), 6.68 (1H, m), 6.14 (1H, d), 4.77 (1H, m), 4.43 (2H, t), 4.08 (2H, m), 3.87 (2H, s), 3.83 (3H, s), 3.34 (2H, d), 2.38 (3H, s), 1.90 (3H, s), 1.78-1,70 (4H, m).

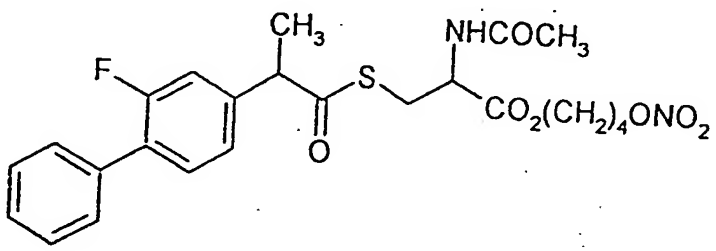
Elementary analysis:

Calculated C: 54.24% H: 4.88% N: 6.80% S: 5.17% Cl: 5.72%

Found C: 54.32% H: 4.93% N: 6.91% S: 5.13% Cl: 5.84%

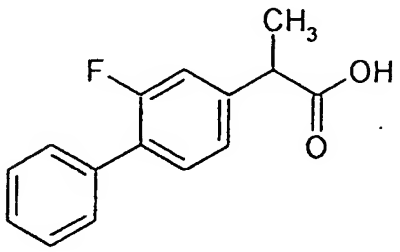
EXAMPLE 4

Synthesis of (S)-N-acetyl-[2-fluoro-α-methyl-(1,1'-biphenyl)-4-acetyl]cisteine 4-(nitroxy)butyl ester (NCX 2131) having formula

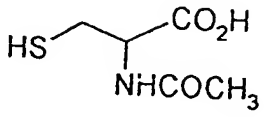


(NCX2131)

The precursor is flurbiprofen (Formula IX), the precursor of B is N-acetylcisteine (formula CVIII)



(IX)



(CVIII)

The NCX 2131 compound is synthetized according to the process described in Example 1. The substance appears as an oil. Yield: 26%

^{1}H-NMR ($CDCl_3$): 7.41-7.38 (6H, m), 7.10 (2H, m), 6.22 (1H, d), 4.78 (1H, m), 4.46 (2H, t), 4.13 (2H, t), 3.92 (1H, q), 3.36 (2H, d), 1.93 (3H, d), 1.76 (4H, d), 1.55 (3H, d).

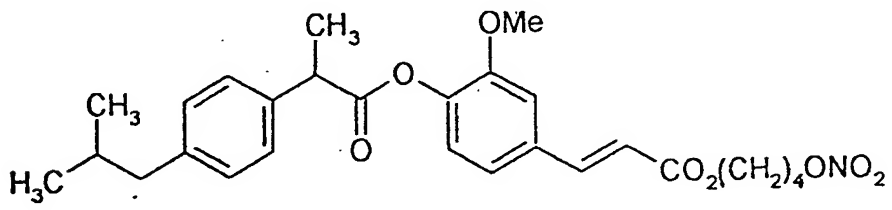
Elementary analysis

Calculated C: 56.91% H: 5.37% N: 5.55% S: 6.33% F: 3.75%

Found C: 56.99% H: 5.41% N:5.66% S: 6.41% F: 3.83%

EXAMPLE 5

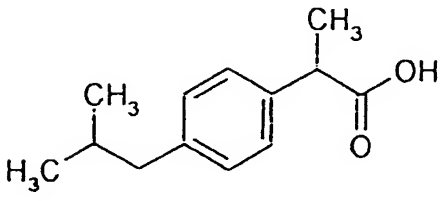
Preparation of trans-3-[4-[α-methyl-[4-(-2-methylpropyl)benzene] acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester (NCX 2210) having formula:



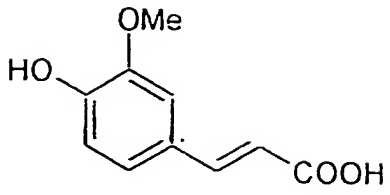
(NCX 2210)

The precursor is ibuprofen (Formula VII), the precursor of

B is ferulic acid (formula DII):



(VII)



(DII)

a) Synthesis of trans-3-[4-[α-methyl-[4-(-2-methylpropyl) benzene]acetyloxy]-3-methoxyphenyl] -2-propenoic acid

To a solution of α-methyl-[4-(2-methylpropyl)benzene]acetic acid (5.03 g, 24.4 mmoles) in tetrahydrofuran (100 ml) and N,N-dimethylformamide (5 ml) 1,1-carbonyldiimidazole (4.25 g, 24.8 mmoles) is added. After 1 hour the obtained solution is treated with ferulic acid (4.90 g, 25 mmoles), sodium ethylate (89 mg) is added and left at room temperature under stirring for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine. The organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure.

The obtained residue is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. 5.1 g of trans-3-[4-[α-methyl-[4-(-2-methylpropyl)benzene] acetyl]-3-methoxyphenyl]-2-propenoic acid as white solid, with m.p. 131°-137°C, are obtained.

^{1}H-NMR ($CDCl_3$): 7.72 (1H, d), 7.32 (2H, dd), 7.26 (1H, m), 7.16-7.07 (4H, m), 6.98 (1H, d), 6.37 (1H, d), 3.99 (1H, q),

3.73 (3H, s), 2.47 (2H, d), 1.88 (1H, m), 1.63 (3H, d), 0.92 (6H, d).

b) synthesis of trans-3-[4-[α-methyl-[4-(-2-methylpropyl-)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester

To a solution of trans-3-[4-[α-methyl-[4-(2-methylpropyl)-benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid (5.33 g, 14 mmoles) in N,N-dimethylformamide (130 ml), sodium ethylate (1.2 g, 16 mmoles) is added under stirring. After 1 hour to the obtained mixture 1,4-dibromobutane (10 g, 46 mmoles) is added and let react at room temperature for 12 hours. The reaction mixture is washed with HCl 5%, then with water and lastly with brine, the organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 4.46 g of trans-3-[4-hydroxy-[α-methyl-[4-(-2-methylpropyl)benzene]acetyl]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester are obtained.

c) Synthesis of trans-3-[4-[α-methyl-[4-(-2-methylpropyl)benze-ne]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester

To a solution of trans-3-[4-[α-methyl-[4-(-2-methylpro-pyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromo-butyl ester (4 g, 7.72 mmoles) in acetonitrile (70 ml) silver nitrate (2.58 g, 15 mmoles) is added. The reaction mixture is

heated under reflux for 2 hours away from light. At the end the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The recovered residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 8/2. 2.4 g of trans-3-[4-[α-methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester as an oil, are obtained.

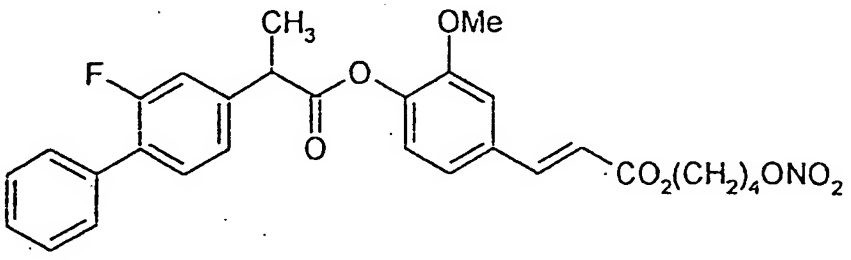
^{1}H-NMR ($CDCl_3$): 7.62 (1H, d), 7.32 (2H, d), 7.15 (2H, d), 7.16-7.05 (2H, m), 6.96 (1H, d), 6.35 (1H, d), 4.51 (2H, t), 4.24 (2H, t), 3.99 (1H, q), 3.74 (3H, s), 2.48 (2H, d), 1.89-1.83 (5H, m), 1.62 (3H, d), 0.92(6H, d).

Elementary analysis:

Calculated	C: 64.91%	H: 6.66%	N: 2.82%
Found	C: 64.83%	H: 6.52%	N: 2.69%

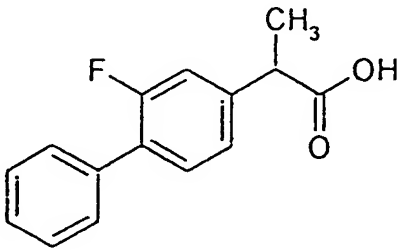
EXAMPLE 6

Synthesis of trans-3-[4-[2-fluoro-α-methyl-(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitroxy) butyl ester (NCX 2216) having formula:

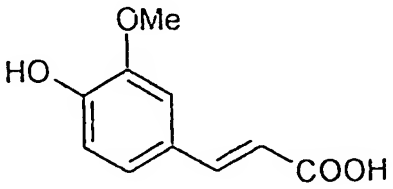


(NCX2216)

The precursor is flurbiprofen (formula IX), the precursor of B is ferulic acid (formula DII)



(IX)



(DII)

The NCX 2216 compound is synthetized according to the process described in Example 5. The total process yield is 32%. The substance appears as an amorphous solid.

^{1}H- NMR ($CDCl_3$): 7.40-7.25 (9H, m), 7.07-7.01 (2H, d), 6.98 (1H, m), 6.38 (1H, d), 4.44 (2H, t), 4.46 (2H, t), 4.21 (2H, t), 4.04 (1H, q), 3.73 (3H, s), 1.72 (4H, m), 1.65 (3H, d).

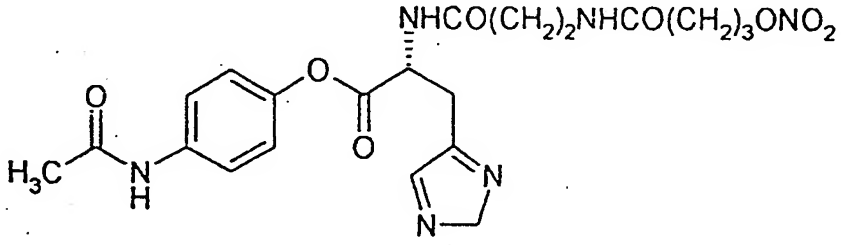
Elementary analysis:

Calculated C: 64.79% H: 5.25% N: 2.62% F: 3.53%

Found C: 64.85% H: 5.31% N: 2.74% F: 3.48%

EXAMPLE 7

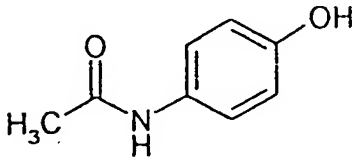
Preparation of N-(4-nitroxybutyryl)-β-alanyl (L)-histidine 4-acetamido phenyl ester (NCX 2160) having formula:



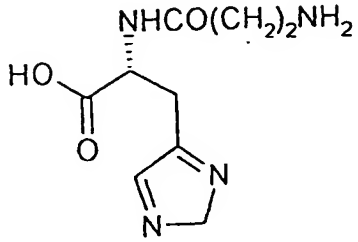
(NCX 2160)

wherein the precursor is acetaminofen (paracetamol) having

formula (X) and the precursor of B is (L)-carnosine (NCX 2053) having formula (CI):



(X)



(CI)

a) Synthesis of N-(4-bromobutyryl)-β-alanyl (L)-histidine

To a solution of carnosine (5 g, 22.1 mmoles) in N,N-dimethylformamide (80 ml), triethylamine (4.62 ml, 33.1 mmoles) and 4-bromobutyrylchloride (chloride of 4-bromobutyric acid - 83.85 ml, 33.1 mmoles) are added. The solution is left under stirring for 24 hours at room temperature, then it is diluted with ethyl acetate and the organic phase is washed with water. The organic phase is then anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel eluting with ethyl acetate, obtaining the final product.

b) synthesis of N-(4-bromobutyryl)-β-alanyl (L)-histidine 4-acetamidophenyl ester

To a solution of N-(4-bromobutyryl)-β-alanyl (L)-histidine (3 g, 8 mmoles) in chloroform (50 ml) and N,N-dimethylformamide (4 ml), paracetamol (1.21 g, 8 mmoles), N,N-dicyclohexyl carbodiimide (1.65 g, 8 mmoles) and dimethylaminopyridine (0.04

g, 0.36 mmoles) are added under stirring. The mixture is let react at room temperature for 6 hours. Lastly it is filtered, diluted with chloroform and washed with water. The organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. N-(4-bromobutyryl)-β-alanyl (L)-histidine 4-acetamido phenyl ester is obtained.

c) Synthesis of N-(4-nitroxybutyryl)-β-alanyl (L)-histidine 4-acetamidophenyl ester

To a solution of N-(4-bromobutyryl)-β-alanyl (L)-histidine 4-acetamido phenyl ester (4 g, 7.87 mmoles) in acetonitrile (70 ml), silver nitrate (1.87 g, 11 mmoles) is added under stirring. The reaction mixture is heated for 5 hours under reflux, away from light. At the end the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7. The expected product is obtained with an yield of 17%.

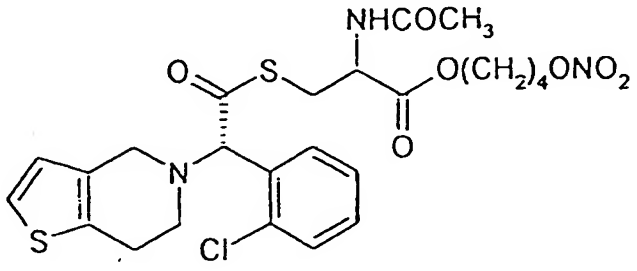
Elementary analysis:

Calculated	C: 51.39%	H: 5.34%	N:17.19%
Found	C: 51.28%	H: 5.28%	N:17.06%

EXAMPLE 8

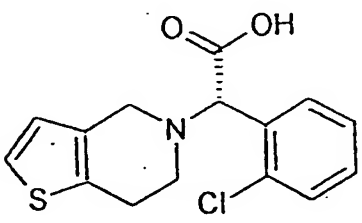
Preparation of N-acetyl-S-[(S)-α-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridin-5(4H)acetyl] (S)-cisteine 4-(nitroxy)

butyl ester (NCX 2136)

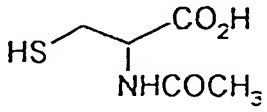


(NCX 2136)

wherein the precursor is clopidogrel having formula (XI) and the precursor of B is N-aceticisteine having formula (CVIII):



(XI)



(CVIII)

The compound is synthetized following the procedure reported in Example 1. The yield is of 23%.

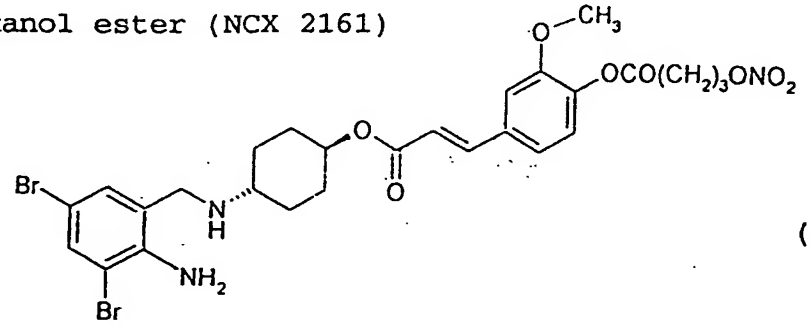
Elementary analysis:

Calculated C: 50.55% H: 4.95% N: 7.40% S: 11.24% Cl: 6.22%

Found C: 50.70% H: 4.99% N: 7.60% S: 11.20% Cl: 6.15%

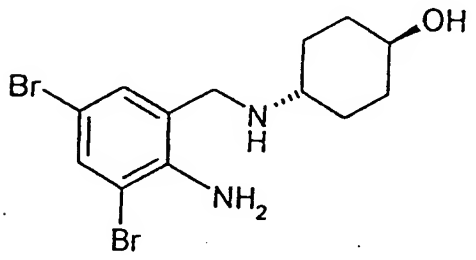
EXAMPLE 9

Preparation of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans-propenoyl-4-[(2- amino-3,5-dibromophenyl)methylamino] cyclohexanol ester (NCX 2161)

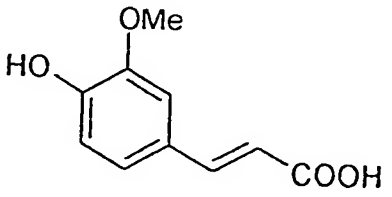


(NCX2161)

wherein the precursor is ambroxol having formula (XII) and the precursor of B is represented by ferulic acid having formula (DII):



(XII)



(DII)

a) Synthesis of 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl)methylamino] trans cyclohexanol

To a mixture of 4-[(2-amino-3,5-dibromophenyl)methylamino-]cyclohexanol (5 g, 13.22 mmoles) in dioxane (35 ml) and water (50 ml), triethylamine (3.31 ml, 23.7 mmoles) and di-ter-butyldicarbonate (3.46 g, 15.86 mmoles) are added under stirring. After 24 hours the solution is concentrated under vacuum, a HCl 1% solution until neutral pH (pH=7) is added and the organic phase is extracted with ethyl acetate. The organic phase is anhydrified with sodium sulphate and evaporated under vacuum. 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol is obtained which is used without further purification.

b) Synthesis of (3-methoxy-4-hydroxyphenyl)-2-trans-propenoyl-

4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl)methylamino] cyclohexanol ester

To a solution of ferulic acid (4 g, 20.5 mmoles) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazol (3.34 g, 20.5 mmoles) is added. After 10 minutes the solution is treated with 4-[(2-ter-butoxycarbonylamino-3,5-dibromophenyl) methyl amino]cyclohexanol (9.8 g, 20.5 mmoles) and let react at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylen chloride, washed with a HCl 1% solution and then with water. The organic phase is anhydrified with sodium sulphate and then evaporated under vacuum. The obtained residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 1/1. (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester, is obtained.

c) Synthesis of [3-methoxy-4-(4-bromobutyryl-oxy)phenyl]-2-trans propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl) methylamino] cyclohexanol ester

To a solution of (3-methoxy-4-hydroxyphenyl)-2-trans propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl) methylamino] cyclohexanol ester (4 g, 6.11 mmoles) in tetrahydrofuran (80 ml), triethylamine (0.85 ml, 6.11 mmoles) and 4-bromobutyrylchloride (0.7 ml, 6.11 mmoles) are added under stirring. It is let react at room temperature for 8 hours and

then the organic solvent is evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate and the organic phase washed with water. The organic phase is anhydrified with sodium sulphate and evaporated under vacuum. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. [3-methoxy-4-(4-bromobutyryloxy)-phenyl]-2-trans propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester is obtained.

d) Synthesis of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans-propenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenyl) methylamino] cyclohexanol ester

To a solution of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoyl-4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl)methylamino] cyclohexanol ester (4 g, 4,98 mmoles) in acetonitrile (70 ml), silver nitrate (0.87 g, 4.98 mmoles) is added under stirring. It is heated under reflux for 7 hours away from light and lastly the formed salt is removed by filtration. The organic solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo-phenyl)methylamino] cyclohexanol ester is obtained.

e) Synthesis of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-

transpropenoyl 4-[(2-amino-3,5-dibromo phenyl) methylamino] cyclohexanol ester

To a solution of [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl 4-[(2-ter-butoxycarbonylamino-3,5-dibromo phenil)-methylamino] cyclohexanol ester (2 g, 2.54 mmoles) in ethyl acetate (50 ml), cooled at 0°C and maintained under stirring, a HCl 5N solution in ethyl acetate (3.17 ml) is added. The solution is left under stirring at 0°C for 4 hours. Lastly the precipitate is filtered. The obtained crude product is treated with ethyl acetate, to which a 5% sodium bicarbonate solution is added. It is shaken and the bicarbonate solution is substituted with an equal part of water. It is shaken again, the organic phase is recovered, anhydrified with sodium sulphate and evaproated at reduced pressure. [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-transpropenoyl-4-[(2-amino-3,5-dibromophenyl) methylamino] cyclohexanol ester is obtained.

Yield: 36%

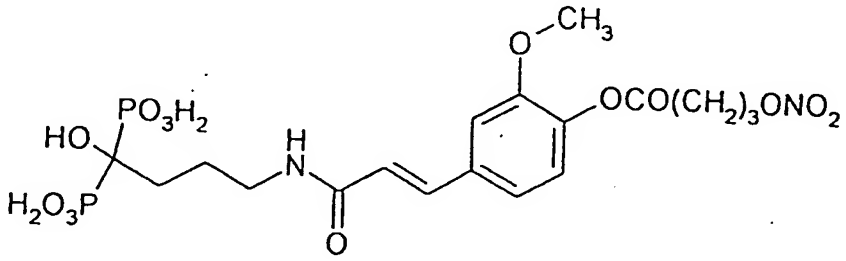
Elementary analysis:

Calculated C: 47.30% H: 4.56% N: 6.15% Br: 23.31%

Found C: 47.26% H: 4.53% N: 6.00% Br: 23.42%

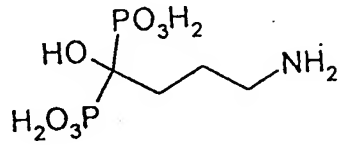
EXAMPLE 10

Preparation of [4-amino-[[3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans propenoyl]-1-hydroxy-butyliden]-bisphosphonic acid (NCX 2211),

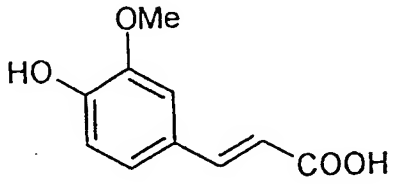


(NCX 2211)

wherein the precursor is alendronic acid of formula (XIII) and the precursor of B is the ferulic acid (formula DII):



(XIII)



(DII)

a) Synthesis of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoic acid

To a solution of ferulic acid (1.2 g, 6.11 mmoles) in tetrahydrofuran (80 ml), triethylamine (0.85 ml, 6.11 mmoles) and 4-bromobutyrylchloride (0.7 ml, 6.11 mmoles) are added under stirring. It is let react at room temperature for 3 hours and then evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate and the organic phase washed with water. The organic phase is then anhydrified with sodium sulphate and evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting

with chloroform/methanol 8/2. The [3-methoxy-4-(4-bromobutyryloxy)-phenyl]-2-trans propenoic acid is lastly isolated.

b) Synthesis of the [3-methoxy-4-(4-nitroxybutyryloxy)phenyl]-2-trans propenoic acid

To a solution of [3-methoxy-4-(4-bromobutyryloxy)phenyl]-2-trans-propenoic acid (1.5 g, 4.5 mmoles) in acetonitrile (70 ml) silver nitrate (0.87 g, 4.98 mmoles) is added under stirring. The mixture is heated under reflux and, under stirring, it is reacted for 3 hours sheltered from the light. The formed salt is removed by filtration and the organic phase is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column, eluting with chloroform/methanol 8/2. The [3-methoxy-4-(4-nitroxybutyroyloxy)phenyl]-2-trans propenoic acid is recovered.

c) Synthesis of [4-amino-[[3-methoxy-4-(4-nitroxy butyryloxy)phenyl]-2-trans propenoyl]-1-hydroxy-butyliden] bisphosphonic acid

To a solution of [3-methoxy-4-(4-nitroxybutyroyloxy)-phenyl]-2-trans propenoic acid (2g, 6.4 mmoles) in N,N-dimethylformamide (30 ml), cooled at 0°C, N,N'dicyclohexylcarbodiimide (1.3 g, 6.4 mmoles) and 1-hydroxybenzotriazol (1.04 g, 7.68 mmoles) are added under stirring. After 30 minutes alendronic acid (1.6 g, 6.4 mmoles) is added. The reaction mixture is left under stirring at room temperature for 7 hours. At the end it is acidified with a HCl 5% solution and the

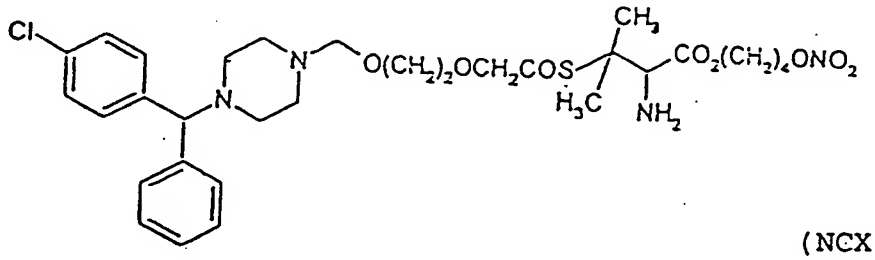
organic phase is extracted with ethyl acetate. The organic phase is washed with brine, annydrified with sodium sulphate and evaporated at reduced pressure. The crude product is purified by chromatography on silica gel column eluting with methylene chloride/methanol 8/2, obtaining the [4-amino-[[3-methoxy-4-(4-nitroxybutyroyloxy)phenyl]-2-trans propenoyl]-1-hydroxy butyliden] bisphosphonic acid. Yield: 11%.

Elementary analysis:

Calculated	C: 19.71%	H: 4.36%	N: 5.07%	P: 11.17%
Found	C: 19.56%	H: 4.28%	N: 5.04%	P: 11.25%

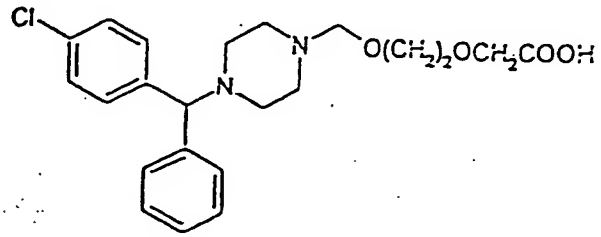
EXAMPLE 11

Preparation of S-[[2-[4-(4-chlorophenyl)phenylmethyl)-1-piperazinyl]ethoxy]acetyl] penicillamine 4-(nitroxy)butyl ester (NCX 2060) having formula

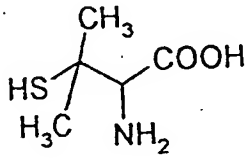


(NCX 2060)

wherein the precursor is cetirizine of formula (XIV) and the precursor of B is penicillamine (formula CV):



(XIV)



(CV)

a) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl] N-ter-butoxycarbonylpenicillamine-4-(nitroxy)butyl ester

The compound is prepared according to the procedure reported in Example 1, by using N-ter-butoxycarbonyl-penicillamine instead of N-acetyl cisteine.

b) Synthesis of S-[[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetyl]-penicillamine-4-(nitroxy)butyl ester.

The compound is obtained from the previous one by following the procedure described in step e) of Example 9 to remove the protective group N-ter-butoxycarbonyl and recover the aminic function. Yield: 26%.

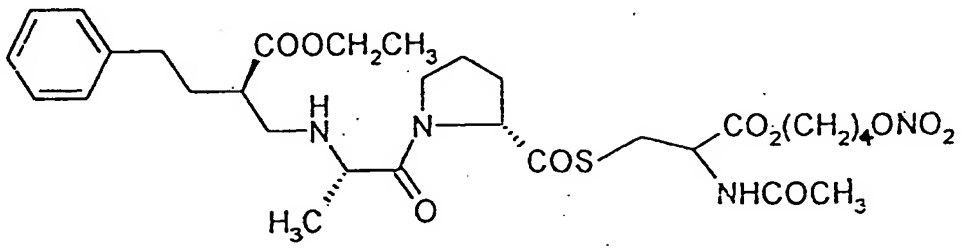
Elementary analysis:

Calculated C: 55.78% H: 6.49% N: 8.43% S: 4.80% Cl: 5.31%

Found C: 55.61% H: 6.31% N: 8.29% S: 4.93% Cl: 5.43%

EXAMPLE 12

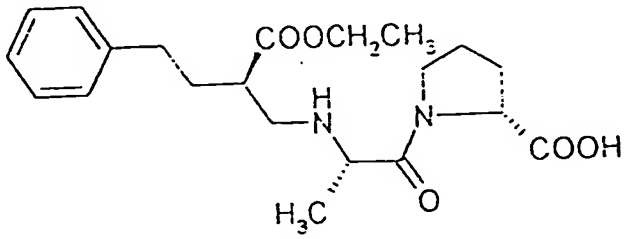
Preparation of N-acetyl-S-[(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-prolin]cisteine 4-(nitroxy)butyl ester of formula (NCX 2134)



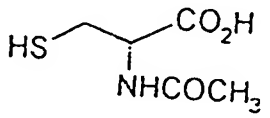
(NCX 2134)

wherein the precursor is enalapril of formula (XV) and the pre-

cursor of B is N-acetylcisteine (formula CVIII):



(XVI)



(CVIII)

The compound is synthetized following the procedure reported in Example 1. Yield: 27%

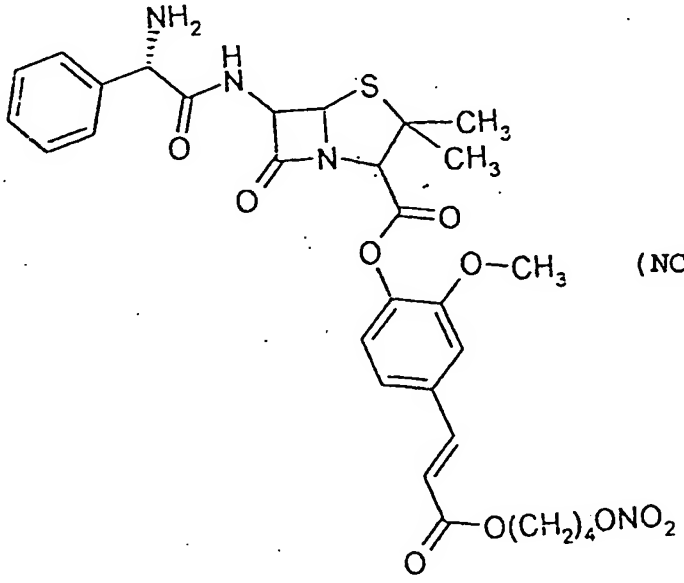
Elementary analysis:

Calculated C: 55.18% H: 6.79% N: 8.62% S: 4.91%

Found C: 55.30% H: 6.85% N: 8.71% S: 4.85%

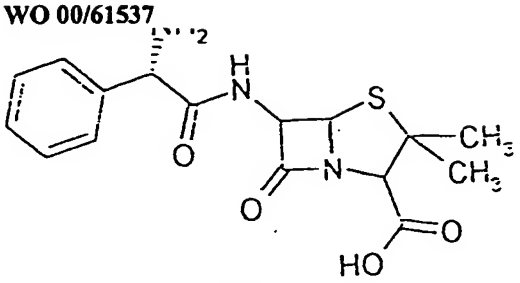
EXAMPLE 13

Preparation of 3-[4- D-α-aminobenzylpenicillaminoyloxy]-3-methoxyphenyl]-2-trans propenoyl 4-(nitroxy)butyl ester (NCX 2080) having formula

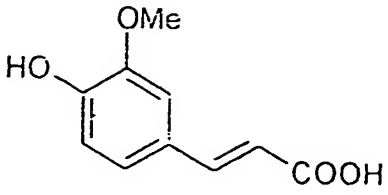


(NCX2080)

wherein the precursor is represented by ampicilline (formula XVI) and the precursor of B is ferulic acid (formula DII):



(XVI)



(DII)

The compound is synthetized following the method reported in Example 5. Yields: 11%.

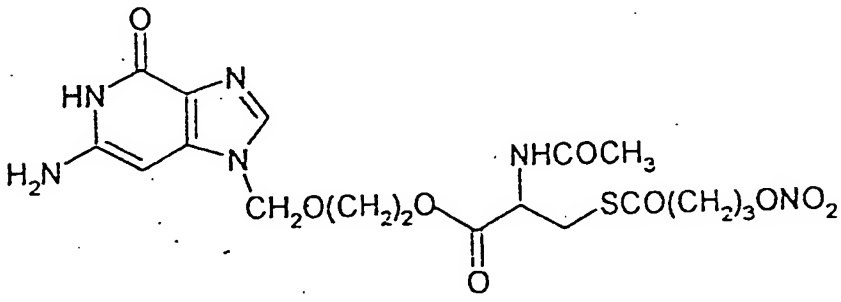
Elementary analaysis

Calculated C: 56.04% H: 5.33% N: 8.75% S: 4.99%

Found C: 56.15% H: 5.48% N: 8.65% S: 4.83%

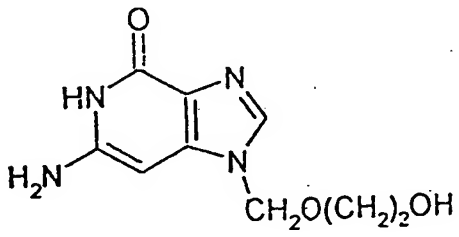
EXAMPLE 14

Preparation of 9-[[2-[-N-acetyl-S-(4-nitroxybutyroyl)cisteinyl]ethoxy]-methyl]guanine of formula (NCX 2135),

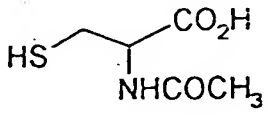


(NCX2135)

wherein the precursor is aciclovir of formula (XVII) and the precursor of B is N-acetylcisteine (formula CVIII):



(XVII)



(CVIII)

a) Synthesis of N-acetyl-S-(4-bromobutyroyl)cisteine

A solution containing 4-bromobutyric acid (5.1 g, 30.6 mmoles) and 1,1'-carbonyldiimidazole (5.61 g, 34.6 mmoles) in chloroform (50 ml) is prepared and it is left under stirring at room temperature for 1 hour. To the reaction mixture a solution of N-acetylcisteine (5 g, 30.6 mmoles) in N,N-dimethylformamide (5 ml) containing sodium ethylate (50 mg) is added. It is let react under stirring and after 24 hours the solution is washed with HCl 1% and then with brine. The organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel column, eluent ethyl acetate/chloroform 7/3, lastly obtaining N-acetyl-S-(4-bromobutyroyl) cisteine.

b) Synthesis of N-acetyl-S-(4-nitroxybutyroyl)cisteine

To a solution of N-acetyl-S-(4-bromobutyroyl)cisteine (3 g, 9.6 mmoles) in acetonitrile (70 ml) silver nitrate (1.7 g, 10 mmoles) is added. The reaction mixture is heated under stirring under reflux for 2 hours away from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate/chloroform 7/3, lastly obtaining N-acetyl-S-(4-nitroxybutyroyl)cisteine.

c) Synthesis of 9-[[2-[N-Acetyl-S-(4-nitroxybutyroyl)cistei-

nyl]ethoxy]methyl]guanine

A solution of N-acetyl-S-(4-nitroxybutyroyl)cisteine (2.8 g, 9.6 mmoles) and 1,1-carbonyldiimidazol (1.55 g, 9.6 mmoles) in tetrahydrofuran (50 ml) is prepared and left under stirring at room temperture for 1 hour. The reaction mixture is treated with aciclovir (2.16 g, 9.6 mmoles). After 6 hours of reaction at room temperature, the solution is evaporated at reduced pressure, the obtained residue treated with ethyl acetate and washed with brine. The organic phase is anhydrified with sodium sulphate and then dried under vacuum. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate. 9-[[2-[N-acetyl-S-(4-nitroxybutyroyl)cisteinyl-]ethoxy]methyl]guanine is obtained. Yields: 9%.

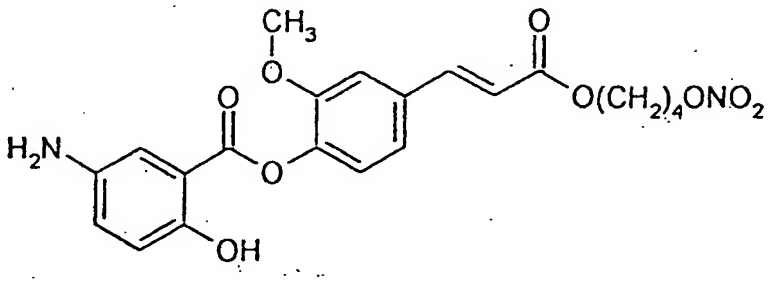
Elementary analysis

Calculated C: 35.25% H: 3.95% N: 13.76% S: 47.05%

Found C: 35.38% H: 3.99% N: 13.84% S: 47.20%

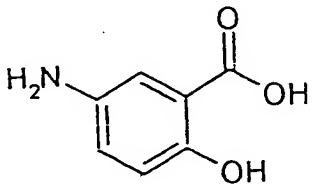
EXAMPLE 15

Preparation of trans-3-[4-(5-amino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoyl 4-(nitroxy) butyl ester (NCX 2212),

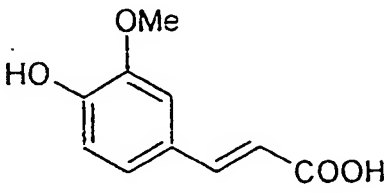


(NCX2212)

wherein the precursor is mesalamine of formula (XVIII) and the precursor of B is the ferulic acid (formula DII):



(XVIII)



(DII)

a) synthesis of trans-3-[4-(5-ter-butyloxycarbonylamino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoic acid 4-(nitroxy)butyl ester

The compound is synthetized according to the procedure reported in Example 5, first protecting the primary aminic group of the mesalamine as described in Example 9, step a).

b) Obtaining of trans-3-[4-(5-amino-2-hydroxybenzoyl)-3-methoxyphenyl]2-propenoyl 4-(nitroxy)butyl ester

The final compound is obtained by hydrolizing the bond between the aminic function and the N-ter-butoxycarbonyl protective group as described in Example 9, step e). Yields: 28%.

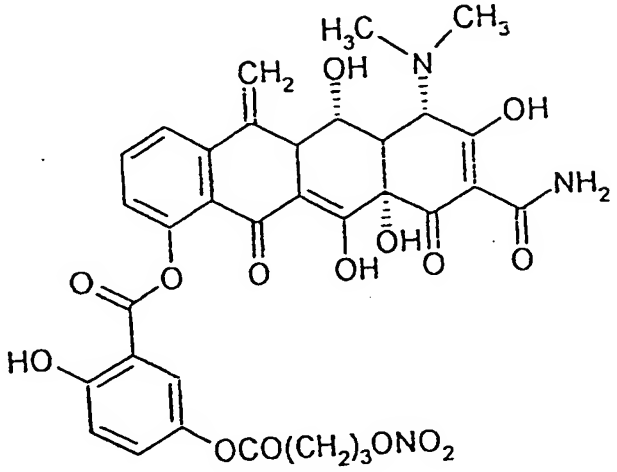
Elementary analysis:

Calculated	C: 56.49%	H: 4.96%	N: 6.30%
Found	C: 56.55%	H: 4.82%	N: 6.45%

EXAMPLE 16

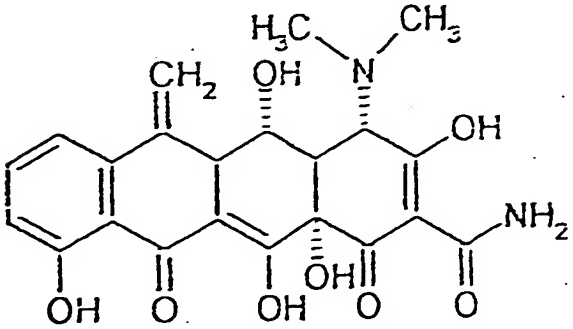
Preparation of 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitro-

xybutyryloxy)benzoyl]tetracycline of formula (NCX 2163)

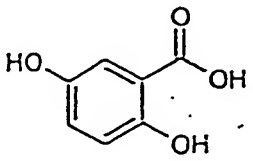


(NCX2163)

wherein the precursor is methacycline of formula (XIX) and the precursor of B is the gentisic acid (formula DIII):



(XIX)



(DIII)

a) Synthesis of the 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid

In a solution of 4-bromobutyrylchloride (3 g, 16.17 mmoles) in tetrahydrofuran (50 ml), cooled at 0°C, triethylamine (4.5 ml, 32.34 mmoles) and then gentisic acid (2.4 g, 16.16 mmoli) are dropped under stirring. It is let react at 0°C

for 4 hours, under stirring, then it is evaporated at reduced pressure. The obtained crude product is treated with ethyl acetate, the organic phase is washed with HCl 1% and then brine. The organic phase is anhydrified with sodium sulphate and dried. The obtained residue is purified by chromatography on silica gel column, eluting with methylene chloride/methanol 95/5, obtaining the 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid.

b) Synthesis of 5-(4-nitroxybutyroyloxy)-2-hydroxybenzoic acid

To a solution of 5-(4-bromobutyryloxy)-2-hydroxy-benzoic acid (3 g, 9.6 mmoles) in acetonitrile (150 ml) silver nitrate (1.7 g, 10 mmoles) is added under stirring. The mixture is heated under reflux for 7 hours away from light. Lastly the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column, eluting with methylene chloride/methanol 95/5. In this way the 5-(4-nitroxybutyryloxy)-2-hydroxy-benzoic acid is isolated at the pure state.

c) Synthesis of 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitroxy-butyryloxy)benzoyl]tetracycline

A solution of 5-(4-nitroxybutyryloxy)-2-hydroxy-benzoic acid (5 g, 16.4 mmoles) and 1,1'-carbonyldiimidazol (2.67 g, 16.4 mmoles) in tetrahydrofuran (70 ml) is maintained under stirring at room temperature for 1 hour. Adriamycin (7.2 g,

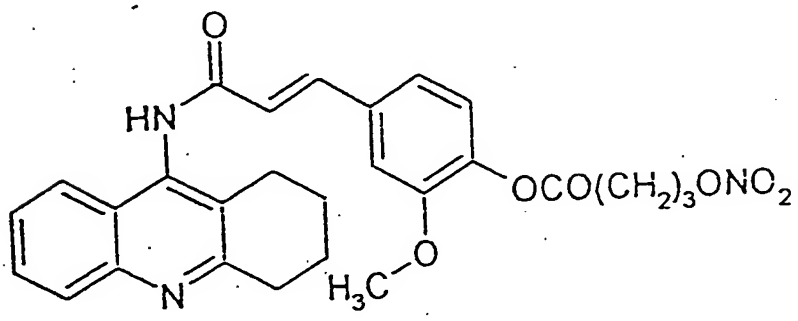
16.4 mmoles) is added. It is reacted under stirring for 12 hours at room temperature. The organic solution is then evaporated at reduced pressure, the obtained residue is treated with ethyl acetate and washed with brine. The organic phase, anhydrified with sodium sulphate, is dried under vacuum. The obtained residue is purified by chromatography on silica gel column eluting with ethyl acetate. 6-methylen-5-hydroxy-10[2-hydroxy-5-(4-nitroxybutyryloxy)benzoyl]tetracycline is obtained. Yield: 19%.

Elementary analysis:

Calculated	C: 55.84%	H: 4.40%	N: 5.95%
Found	C: 55.95%	H: 4.55%	N: 5.98%

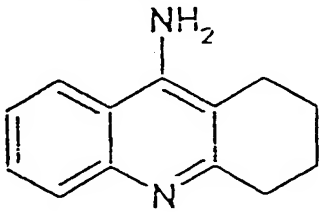
EXAMPLE 17

Preparation of 5-[[3-[3-methoxy-4-(4-nitroxy)butyryloxy]phenyl-2-trans-propenoyl]amino]-1,2,3,4-tetrahydroacridine (NCX 2214)

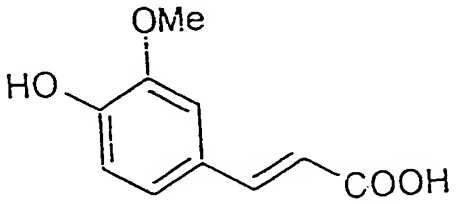


(NCX2214)

wherein the precursor is tacrine of formula (XX) and the precursor of B is the ferulic acid (formula DII):



(XX)



(DII)

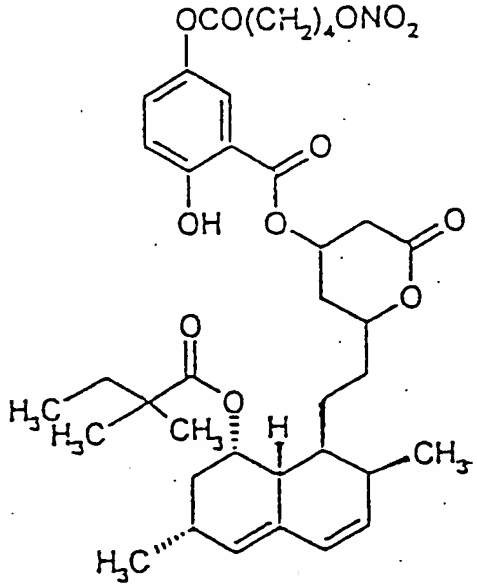
The compound is synthetized according to the procedure reported in Example 10. Yield: 7%.

Elementary analysis:

Calculated	C: 64.13%	H: 5.38%	N: 8.34%
Found	C: 64.28%	H: 5.46%	N: 8.47%

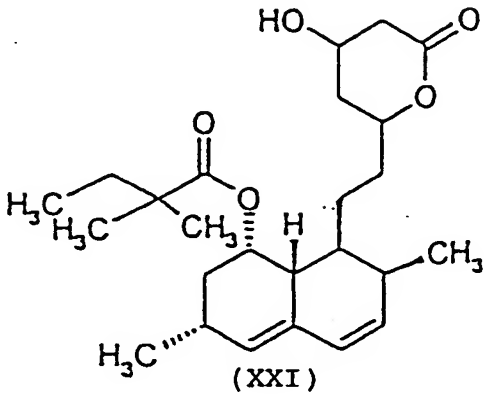
EXAMPLE 18

Preparation of [1S-[1α,3α,7β,8β,(2S*,4S*)]]-2,2-dimethylbutanoic acid 1,2,3,7,8,8-hexahydro-3,7-dimethyl-8-[tetrahydro-4-[2-hydroxy-5-(4-nitroxybutyryloxy) benzoyl-oxy[-6-oxo-2H-piran-2-yl]ethyl]-1-naphthalenyl ester (NCX 2164)

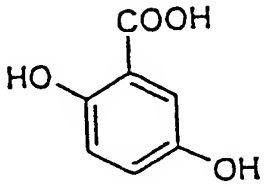


(NCX2164)

wherein the precursor is simvastatine of formula (XXI) and the precursor of B is the gentisic acid (formula DIII):



(XXI)



(DIII)

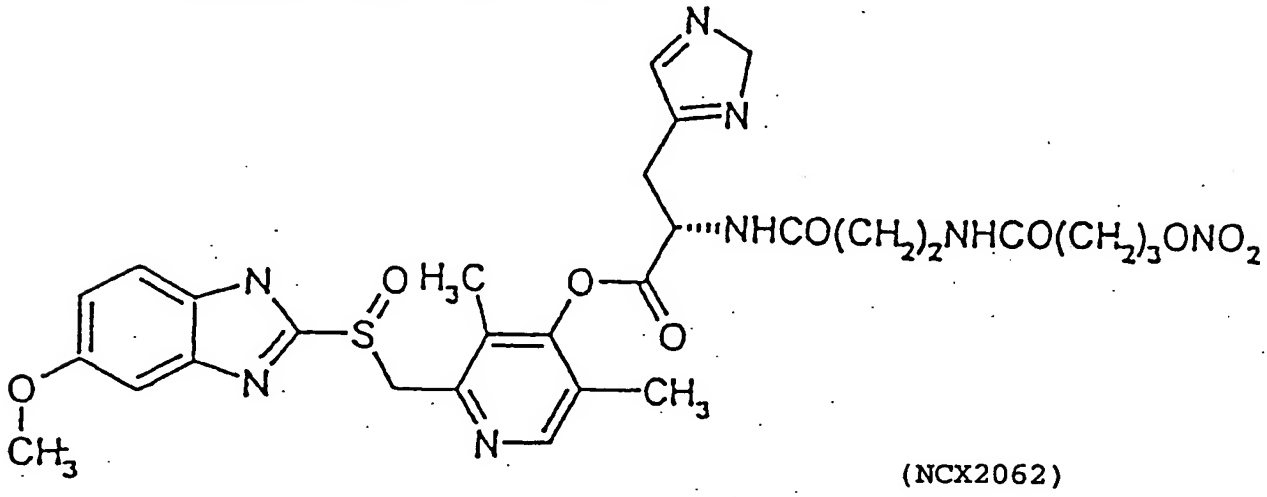
The compound is synthetized following the method described in Example 16. Yield: 13%.

Elementary analysis:

Calculated	C: 63.50%	H: 7.06%	N: 2.01%
Found	C: 63.68%	H: 7.21%	N: 2.19%

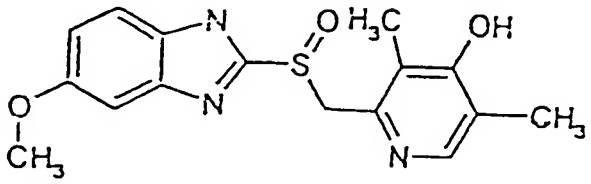
EXAMPLE 19

Preparation of 5-methoxy-2-[[[4-[N-[4-(nitroxy)butyl-β-alanyl](L)-histidinyloxy]-3,5-dimethyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazol (NCX 2062)

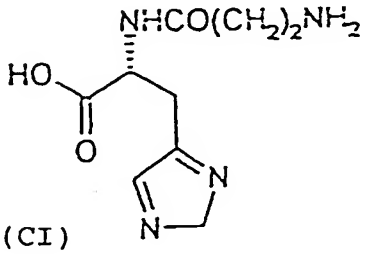


(NCX2062)

wherein the precursor is 4-hydroxyomeprazol of formula (XXII), obtained by treating omeprazol as described in Acta Chem. Scand. 43, 6 1989 pages 549-568 and the precursor of B is carnosine (formula CI):



(XXII)



(CI)

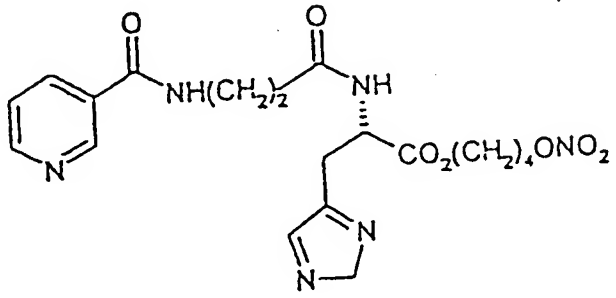
The compound is synthetized according to the process described in Example 7. Yield: 25%

Elementary analysis:

Calculated	C: 51.97%	H: 4.96%	N: 16.79%	S: 4.78%
Found	C: 51.81%	H: 4.80%	N: 16.68%	S: 4.92%

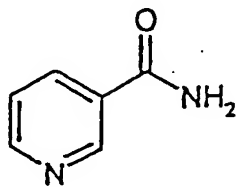
EXAMPLE 20

Preparation of N-nicotinoyl-β-alanyl (L)-histidine 4-(nitroxy)butyl ester (NCX 2073)

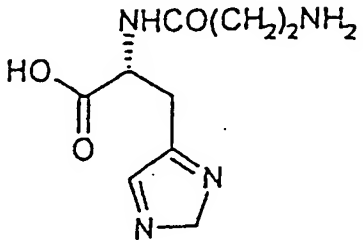


(NCX2073)

wherein the precursor is nicotinamide of formula (XXIII) and the precursor of B is carnosine (formula CI):



(XXIII)



(CI)

a) Synthesis of N-nicotinoyl-β-alanyl (L)-histidine

To a solution of nicotinic acid (2.5 g, 20.5 mmoles) in tetrahydrofuran (40 ml) cooled at 0°C, 1,1'-carbonyldiimidazol (3.34 g, 20.5 mmoles) is added under stirring. After 10 minutes to the solution (L)-carnosine (4.6 g, 20.5 mmoles) is added and it is left under stirring at room temperature for 4 hours. The reaction mixture is concentrated under vacuum, treated with methylene chloride, washed with HCl 1% and then with water. The organic phase is anhydrified with sodium sulphate and evaporated under vacuum. The obtained residue is chromatographed on silica gel column, eluting with ethyl acetate. N-nicotinoyl-β-alanyl (L)-histidine is recovered.

b) Synthesis of N-nicotinoyl-β-alanyl (L)-histidine 4-bromobutyl ester

To a solution of N-nicotinoyl-β-alanyl-(L)-histidine (9.9 g, 30.1 mmoles) in tetrahydrofuran (200 ml) triphenylphosphine (23.7 g, 90.3 mmoles) and carbon tetrabromide (28.85 g, 90.3 mmoles) are added under stirring. The reaction mixture is left under stirring at room temperature for 24 hours. Lastly the solvent is removed by evaporation at reduced pressure. The obtained crude product is purified by chromatography on silica gel column eluting with n-hexane/ethyle acetate 1/1. N-nicotinoyl-β-alanyl-(L)-histidine 4-bromobutyl ester is obtained.

c) Synthesis of N-nicotinoyl-β-alanyl (L)-histidine 4-nitroxybutyl ester

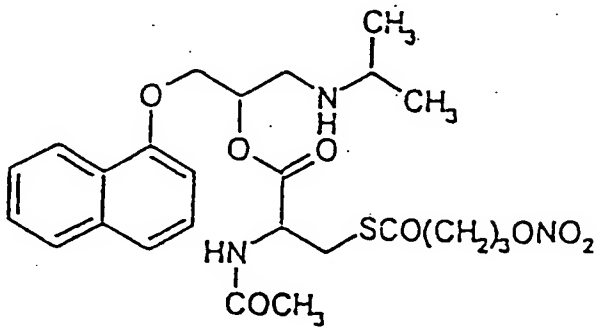
To a solution of N-nicotinoyl-β-alanyl (L)-histidine 4-bromobutyl ester (0.91 g, 1.96 mmoles) in acetonitrile (20 ml) silver nitrate (0.66 g, 3.92 mmoles) is added under stirring. The reaction mixture is heated to reflux under stirring for 4 hours away from light. Lastly the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/1. N-nicotinoyl-β-alanyl-(L)-histidine 4-nitroxybutyl ester is obtained. Yields: 32%.

Elementary analysis:

Calculated	C: 49.50%	H: 5.54%	N: 19.32%
Found	C: 49.35%	H: 5.28%	N: 19.17%

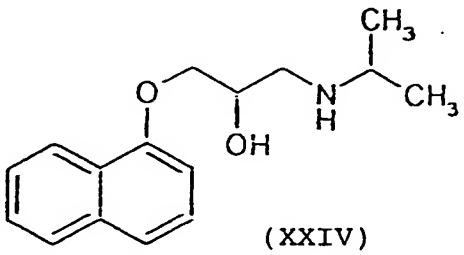
EXAMPLE 21

Preparation of N-acetyl-S-(4-nitroxybutyroyl) cisteine 1-[(1-methylethyl) amino]-3-(1-naphthalen oxy)-2-propanol ester (NCX 2132)

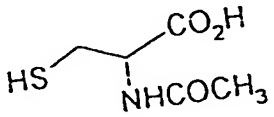


(NCX2132)

wherein the precursor is propranolol of formula (XXIV) and the precursor of B is N-acetylcisteine (formula CVIII):



(XXIV)



(CVIII)

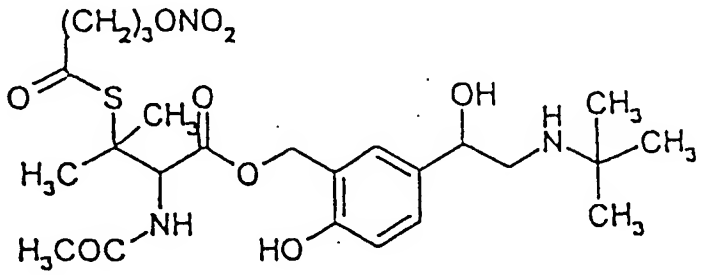
The compound is synthetized with the process described in Example 14. Yields: 7%.

Elementary analysis:

Calculated	C: 56.04%	H: 6.21%	N: 7.88%	S: 5.98%
Found	C: 56.13%	H: 6.35%	N: 7.91%	S: 6.04%

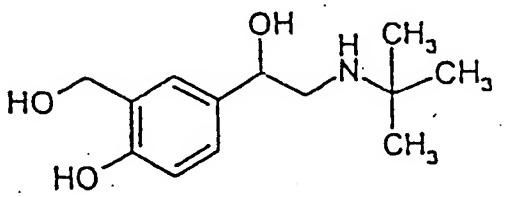
EXAMPLE 22

Preparation of 2-(ter-butylamino)-1-[4-hydroxy-3-[N-acetyl-S-(4-nitroxybutyryl)-penicillaminoyl] oxyphenyl]ethanol (NCX 2133)

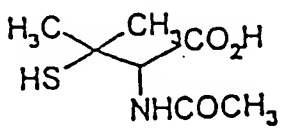


(NCX2133)

wherein the precursor is salbutamol (albuterol) of formula (XX-V) and the precursor of B is N-acetylpenicillamine (formula CV):



(XXV)



(CV)

The compound is synthetized by following the procedure reported in Example 14, using N-acetyl penicillamine instead of N-acetylcisteine. Yields: 43%

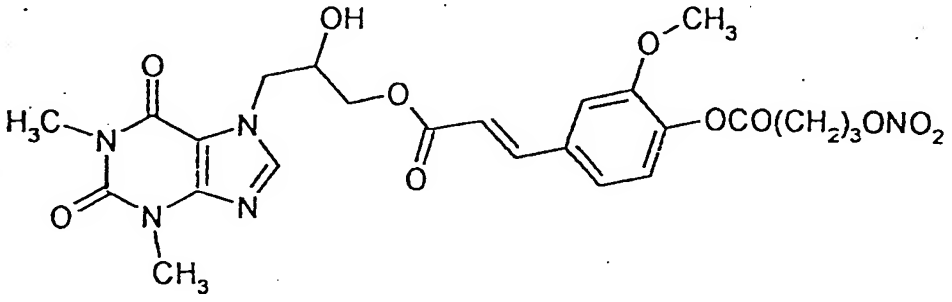
Elementary analysis:

Calculated C: 53.01% H: 6.86% N: 7.76% S: 5.89%

Found C: 53.19% H: 6.80% N: 7.66% S: 5.72%

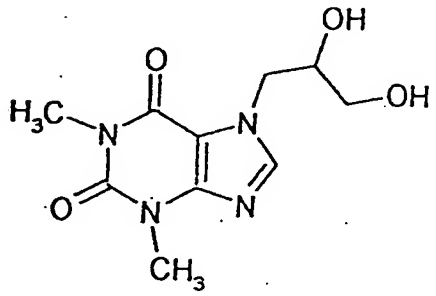
EXAMPLE 23

Preparation of 7-[2-hydroxy-3-[3-methoxy-5-(4-nitrooxybutyryloxy)benzoyl] trans-2-propenoyl]theophylline (NCX 2213)

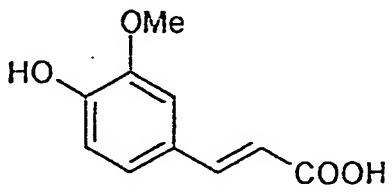


(NCX2213)

wherein the precursor is the diphylline of formula (XXVI) and the precursor of B is the ferulic acid (formula DII):



(XXVI)



(DII)

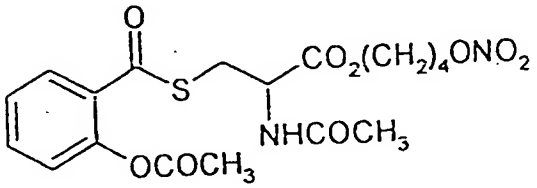
The drug is synthetized according to the process described in Example 9. Yield: 22%

Elementary analysis:

Calculated	C: 51.31%	H: 4.84%	N: 12.52%
Found	C: 51.50%	H: 4.91%	N: 12.68%

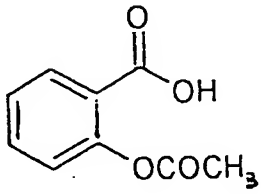
EXAMPLE 24

Preparation of N-acetyl-S-(2-acetylbenzoyl)cisteine 4-(nitro-xy)butyl ester (NCX2138) of formula

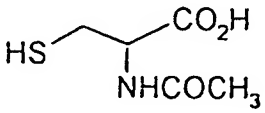


(NCX2138)

wherein the precursor is acetylsalicylic acid of formula (XX-VII) and the precursor of B is N-acetylcisteine (formula CVII-I):



(XXVII)



(CVIII)

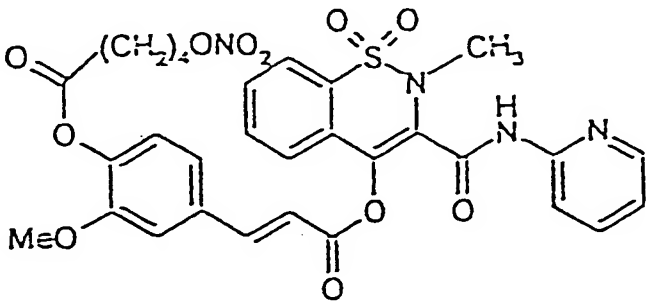
The compound is synthetized according to the process described in Example 1. Yield 36%.

Elementary analaysis

Calculated	C: 48.85%	H: 5.01%	N: 6.36%	S: 7.24%
Found	C: 48.75%	H: 5.02%	N: 6.28%	S: 7.12%

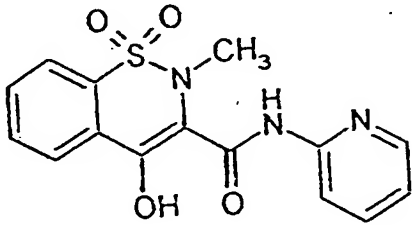
EXAMPLE 25

Preparation of 4-[3-[3-methoxy-5-(4-nitroxybutyryloxy)phenyl]-2-propenoyloxy]-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide (NCX2215)

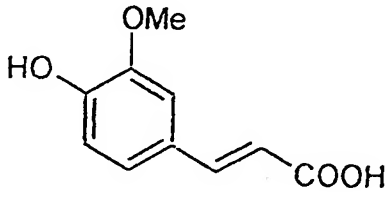


(NCX2215)

wherein the precursor is piroxicam of formula (XXVIII) and the precursor of B is ferulic acid (formula DII):



(XXVIII)



(DII)

The compound is synthetized according to the process reported in Example 9. Yield 18%.

Elementary analysis

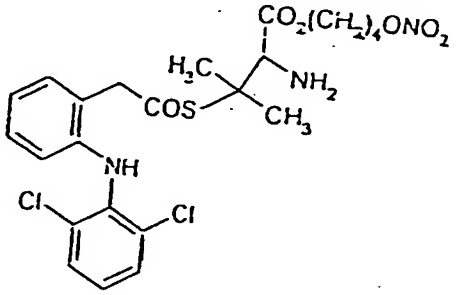
Calculated C: 55.11% H: 4.47% N: 8.60% S: 4.90%

Found C: 55.18% H: 4.52% N: 8.71% S: 4.98%

EXAMPLE 26

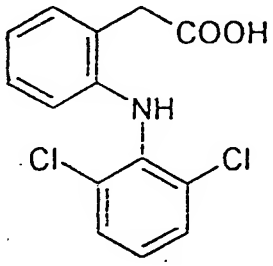
Preparation of S-[2-[(2,6-dichlorophenyl)amino)benzeneaceti-

loxy]penicillamine 4-(nitroxy)butyl ester (NCX 2061) of formula

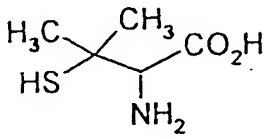


(NCX2061)

wherein the precursor is diclofenac of formula (XXIX) and the precursor of B is penicillamine (formula CV):



(XXIX)



(CV)

The compound is synthetized according to the process described in Example 11. Yield 21%.

Elementary analysis

Calculated C: 50.72% H: 5.00% N: 7.75% S: 5.89% Cl: 13.02%

Found C: 50.61% H: 4.89% N: 7.81% S: 6.01% Cl: 13.21%

PHARMACOLOGICAL TESTS

EXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared, even after administration of a 100 mg/Kg dose.

EXAMPLE F1

Test 1 - experimental model in vivo with N-ethylmaleimide (NEM): study of the gastric tolerability of some drugs screened as precursors of the compounds of the invention.

The animals (rats, weight about 200 g) are distributed in the following groups (No. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + NEM,

B) Groups administered with each drug:

group I: treatment: carrier + drug,

group II: treatment: carrier + drug + NEM.

The drugs assayed in this experiment are the following (Table I): indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine, omeprazol, misoprostol.

Indomethacin, ambroxol and alendronate are administered by os, mesalamine by intracolonic (rectal) route and tacrine, omeprazol, misoprostol by subcutaneous route.

The maximum tolerated dose, determined by administering

each substance by the above said routes to the animals not treated with NEM, is reported in Table I. With higher doses than those reported in the Table, enteropathy, diarrhoea, depression, tremor and sedation have appeared in the animals.

In this experimental model the animals are at first treated with NEM by subcutaneous injection at a dose of 25 mg/kg in physiologic solution. The drug is administered one hour later, in suspension in the carrier. Animals are sacrificed after 24 hours and evaluation of the damage to the gastrointestinal mucosa is made by counting the number of rats, inside each group, with lesions to the stomach at a visual inspection. The total number of said rats is then divided by the total number of rats of the group and multiplied by 100. The thus obtained percentages are reported in Table I. The Table shows that in the groups of rats treated with said drugs without NEM, no gastric lesions were detectable.

All the rats of group II (treated with NEM) showed gastric lesions after administration with the following drugs: indomethacin, ambroxol, mesalamine, sodic alendronate, tacrine. Said drugs therefore can be used in the synthesis of the products of the invention.

Omeprazol and misoprostol cannot instead be used, on the basis of the results provided in test 1, for preparing the products of the invention.

EXAMPLE F2

Test 2 (in vitro): inhibition of apoptosis (DNA fragmentation) induced in the endothelial cells by CIP in the presence of some drugs screened as precursors of the compounds of the invention.

The following precursor drugs (Table II): indomethacin, paracetamol, clopidogrel, salbutamol, ambroxol, sodic alendronate, diphylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, mesalamine, tacrine, simvastine, omeprazol have been tested.

Human endothelial cells of the umbilical vein are prepared according to a standard method. Fresh umbilical veins are filled with a collagenase solution 0.1% by weight and incubated at 37°C for 5 minutes.

Subsequently the veins are perfused with the medium M 199 (GIBCO, Grand Island, NY) pH 7.4 with 0.1% (weight/volume) of collagenase, added with 10% of bovine fetus serum (10 mcg/ml), sodium heparin (50 mcg/ml), thimidine (2.4 mcg/ml), glutamine (230 mcg/ml), penicillin (100 UI/ml), streptomycin (100 mcg/ml) and streptomycin B (0.125 mcg/ml). The cells are collected from the perfusate by centrifugation at 800 rpm and harvested in culture flasks T-75, pretreated with human fibronectin. Cells are then harvested in the same medium, added with bovine hypothalamic growth factor (100 ng/ml). When the cells of the primary cell culture (the cells directly removed from ex-vivo umbilical vein) form a single layer of

confluent cells (about 8,000,000 cells/flask), harvesting is stopped and the layers are washed and trypsinized. The cellular suspensions are transferred into wells of a culture plate having 24 wells, half of said wells being added with the same culture medium containing the drug at a 10^{-4}M concentration, and harvested in a thermostat at 37°C at a constant moisture (90%), CO_2 = 5%. When the drug is not soluble in the culture medium, it is formerly dissolved in a small amount of dimethylsulphoxide. The maximum amount of dimethylsulphoxide which can be added to the culture medium is 0.5%. Only the cells coming from these first subcultures are used for the tests with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by the specific immunological reaction towards factor VIII; these cultures did never show contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a standard physiologic solution buffered with phosphate 0.1 M pH 7.0, at the temperature of 37°C. The content of each well is then incubated for one hour with a CIP suspension in the culture medium at a 5 mM concentration. Evaluation of the cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation in the cultures containing the drug + CIP with respect to the controls treated

with CIP only. Said % variation of DNA fragmentation is determined by evaluating the fluorescence variation by a BX60 Olympus microscope (Olympus Co., Roma) set at the wave length of 405-450 nm, of the test samples with respect to the optical density of the controls. The fluorescence of each sample was determined on 5 replicates. Statistic evaluation has been made with t Student test ($p < 0.01$).

Results are given in Table II and show that indomethacin, paracetamol, clopidogrel, salbutamol, sodic alendronate, diphylline, cetirizine, enalapril, nicotinamide, ampicilline, aciclovir, tacrine, omeprazol do not significantly inhibit apoptosis; these drugs can therefore be used for preparing the products of the invention.

On the contrary ambroxol, mesalamine and simvastatine inhibit apoptosis. Therefore on the basis of the results of test 2 these compounds could not be used for preparing the products of the invention.

EXAMPLE F3

Test 3 - experimental in vivo model with N^{W}-nitro-L-arginine-methyl ester (L-NAME): gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase) and cardiovascular (blood pressure) tolerability of some drugs screened as precursors of the compounds of the invention.

The experimental model adopted is according to J. Clin.

Investigation 90, 278-281,1992.

The endothelial dysfunction is evaluated by determining the damage induced by L-NAME administration to the gastrointestinal mucosa, the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage as blood hypertension.

The animals (rats, average weight 200 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, physiologic solution when by parenteral route),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs used in the test are paracetamol, doxorubicine, simvastatine, omeprazol and misoprostol. Each drug is administered once a day for 4 weeks.

The maximum tolerated dose of the drug being administered to the animals is determined by evaluating, in a separate dose

scaling up experiment on untreated animals, the appearance in the animals of symptoms such as enteropathy, diarrhoea, depression, tremor, sedation.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood pressure is determined and a blood pressure increase is taken as an indication of a damage being occurred to vascular endothelium.

The damage to the gastric mucosa is evaluated as previously mentioned in test 1 (ex. F1). The hepatic damage is determined by evaluation after the sacrifice of the glutamic-pyruvic transaminase (GPT increase).

The drug meets test 3 and it can therefore be used for preparing the compounds of the invention, when in the group of rats treated with L-NAME + drug + carrier, an higher hepatic damage (higher GPT values) and/or higher gastric damage and/or higher cardiovascular damage (higher blood pessure) are found in comparison with the group treated with the carrier only, or the group treated with carrier + drug, or the group treated with carrier + L-NAME.

The test results are reported in Table IV. The % gastric lesions have been determined as in Test 1. The % GPT and % blood pressure values are referred to the corresponding value found in the animals of the 1st group of the control groups. The average value of the blood pressure in this group was of

105 ± 8 mmHg.

The results obtained show that paracetamol, doxorubicin and simvastatine cause hepatic damage and gastroenteropathy (GPT values and the gastric lesions are % higher compared both with the corresponding groups treated with the drug, in the absence of L-NAME, and with the controls treated with L-NAME).

These drugs can therefore be used for preparing the products of the invention.

Omeprazol and misoprostol should not instead be used, on the basis of this test, for preparing the products of the invention.

EXAMPLE F4

Test 4: inhibition of the radical production from DPPH of some substances to be used as precursors of B or B1 (ref. Formulas I and II of the invention)

The method is based on a colorimetric test in which DPPH (2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100 μM are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave

length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, or antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound meets test 4 if radical production inhibition, as above defined, is equal to or higher than 50%.

In Table V the results obtained with the following substances are reported: N-acetylcisteine, cisteine, ferulic acid, (L)-carnosine, gentisic acid.

Table V shows that N-acetylcisteine, cisteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals formed from DPPH by more than 50%.

EXAMPLE F5

Antiinflammatory activity and gastric tolerability of the compounds according to the invention in comparison with the corresponding precursor drugs in conditions of endothelial dysfunction induced by L-NAME (N^W-nitro-L-arginine-methyl ester)

The experimental model of Edwards et Al., J. Pathol. 134, 147-156, 1981 was followed.

Groups formed by 10 rats, having an average weigh of 200 g, have been constituted. The groups have been treated with L-NAME dissolved in drinking water (400 mg/l) for two weeks, except one group which constituted the control group.

The drugs were administered by os, at the dose of 10 mg/Kg, in carrier carboxymethylcellulose 1% in water, 5 ml/Kg.

Thus the groups, except the below described control groups, were treated with the drug + L-MAME + carrier.

The following control groups were formed:

1° control group: treatment: carrier.

2° control group: treatment: carrier + L-NAME.

The drugs used in the experiment are the following: diclofenac and the corresponding thioester with (4-nitroxy)butyryl penicillamine (Ex. 26), piroxicam and the corresponding ester with the p-(4-nitroxy)butyryloxy-ferulic acid (Ex. 25), the acetylsalicylic acid and the corresponding thioester with N-acetyl-(4-nitroxy)butyrylcisteine (Ex. 24).

After two weeks from the beginning of the experiment the animals were subjected to three consecutive injections of air by subcutaneous route, in the dorsal part of the animal, according to the following procedure:

- first injection: 20 ml,
- after three days from the first injection: 10 ml.

- after 6 days from the first injection: the same amount of 10 ml.

The animals were then fasted until the following morning. One hour before the percutaneous injection with carragenine (2 ml of a 1% carragenine solution in water) in the inflammatory exudate, the treated animals received by os the carrier or one of the tested compounds dissolved or suspended in the carrier. The animals were sacrificed after 6 hours from the injection of the carragenine solution. The inflammatory exudate was collected and measured to evaluate the leucocyte infiltration.

In Table VI the antiinflammatory activity is expressed as % inhibition of the leucocyte infiltration with respect to the leucocyte infiltration value found in the animals treated with the carrier and pretreated with L-NAME, the % inhibition of the gastrointestinal damage was evaluated as previously described in Test 1 (ex. 1), and the % blood pressure was evaluated one hour before the sacrifice and referred to that of the 1st control group (treatment: carrier). In this group of animals the average pressure value was of 108 ± 10 mmHg.

Table VI shows that the compounds of the invention are as active as the corresponding precursors in the antiinflammatory activity test, but in the confront of the latter they reduce the damage to the cardiovascular endothelium (lower % increase of blood pressure with respect to that of the corresponding precursor), and besides reduce, or do not give at all, gastric

damage.

EXAMPLE F6

In a second apoptosis experiment indomethacin and the indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cisteine (Ex. 3) according to the present invention were compared. The results are reported in Table III, and show that the compound of the invention inhibits, differently from the precursor, the apoptosis induced by cumene hydroperoxide (CIP).

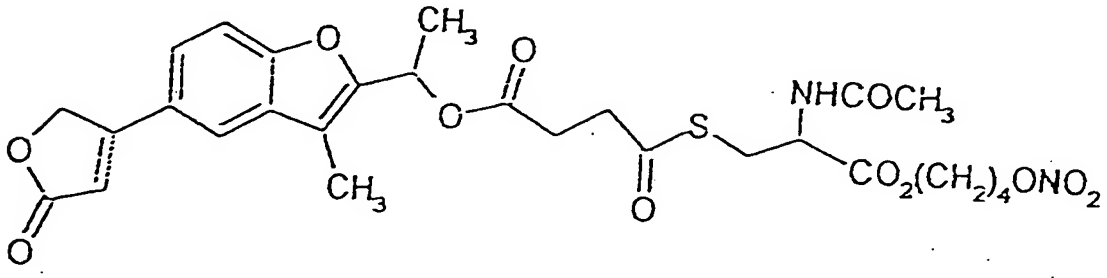
EXAMPLE F7

Gastric tolerability of some drugs used as precursors and of the corresponding compounds according to the invention.

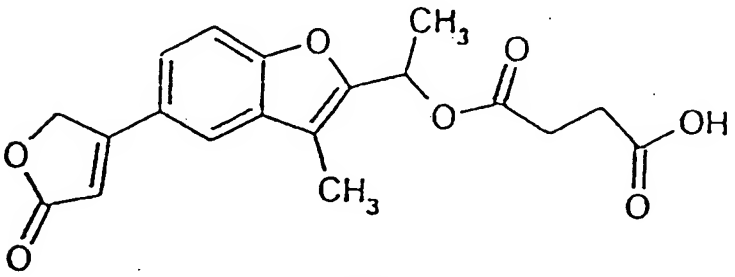
The test for gastrointestinal damage of Example F5 was repeated but omitting the pretreatment of animals with L-NAME. The tested drugs, thereof administered doses and results are reported in Table VII. From the Table it is drawn that gastropathy incidence is much lower in the groups treated with the compounds of the invention in the confront of the groups treated with the corresponding precursors.

EXAMPLE 27

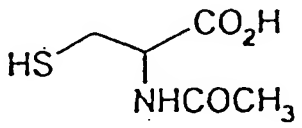
Synthesis of (S)-N-acetyl-S-[[1-[5-(2,5-dihydro-5-oxo-3-furanyl)-3-methyl-2-benzofuranyl]ethyloxy]-4-oxo-butanoyl] cysteine (4-nitroxy)butyl ester of formula



wherein the precursor is benfurodil hemisuccinate of formula (XXXI) and the precursor of B is N-acetylcysteine (formula CVIII)



(XXXI)



(CVIII)

The compound is synthetized according to the process described in Example 4. Yield 25%.

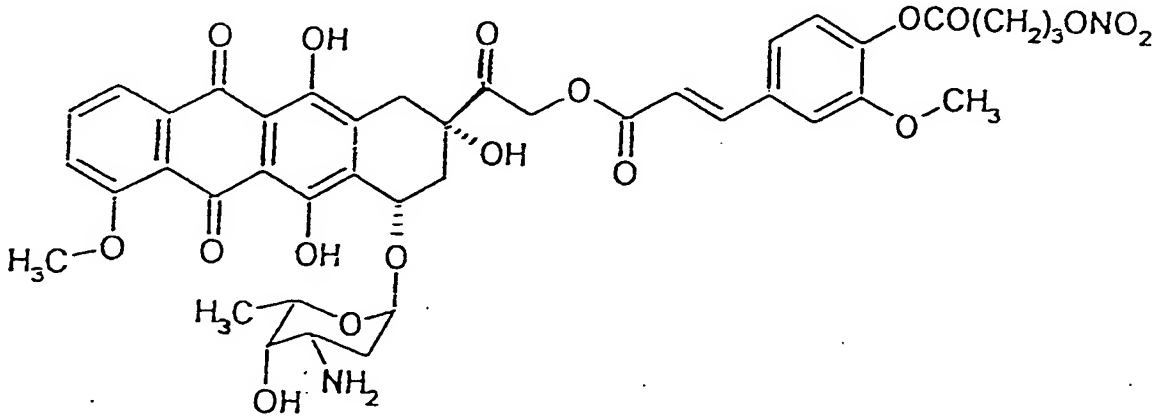
Elementary analysis

Calculated C: 54.19% H: 5.20% N: 4.51% S: 5.17%

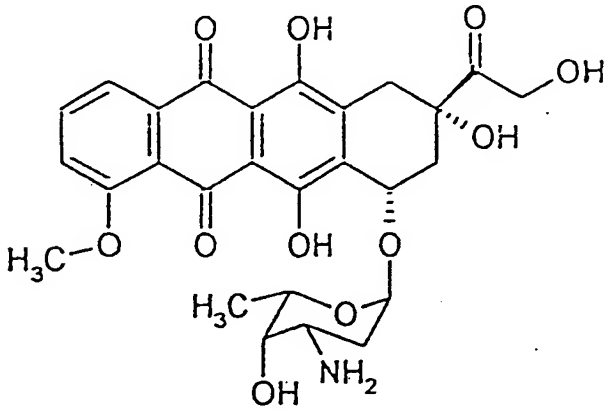
Found C: 54.25% H: 5.22% N: 4.47% S: 5.15%

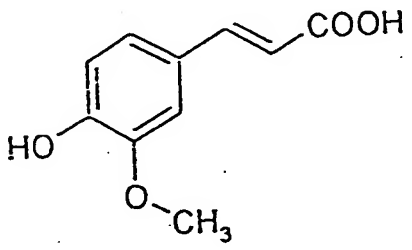
EXAMPLE 28

Synthesis of (8S-cis)-10[(3-amino,2,3,6-tri-deoxy-α-L-lyxo-exo pyranosyl)oxy]-7,8,9,10-tetrahydro,6,8,11-trihydroxy-8-[[[3-methoxy-4-(4-nitroxybutanoyl)phenyl]-2-trans-propenoyl-oxy] methyl-oxo]-1-methoxy-5,12-naphtacenedione of formula



wherein the precursor is doxorubicin of formula (XXXII) and the precursor of B is ferulic acid of (formula DII)





(XXXII) (DII)

The compound is synthetized according to the process described in Example 9. Yield 11%.

Elementary analysis

Calculated	C: 57.88%	H: 4.98%	N: 3.29%
Found	C: 57.91%	H: 5.02%	N: 3.27%

EXAMPLE F8

Example F1 was repeated with four groups of rats (each group of of ten animals), all of them receiving NEM, and orally administered as it follows :

a. control group : the vehicle formed of an aqueous suspension 1% w/v of carboxymethylcellulose,

b. one group (group b - comparative) administered at the same time with 5 mg/Kg (0.014 mmoles/Kg) of indomethacin + 2.3 mg/Kg (0.014 mmoles/Kg) of N-acetylcysteine in the same above vehicle,

c. one group (group c - comparative) administered at the same time with 6.6 mg/Kg (0.014 mmoles/Kg) of indomethacin 4-(nitroxy)butyl ester, synthetized according to the method disclosed in WO 95/09831, + 2.3 mg/Kg (0.014 mmoles/Kg) of N-acetylcysteine in the same above vehicle,

d. one group (group d) administered with 8,7 mg/Kg (0.014 mmoles/Kg) of the indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cisteine (ref. Ex. 3), in the above same vehicle.

The results are reported in Table VIII and show that the mixtures administered respectively to groups b and c (comparatives), differently from the compound of the invention administered to group d, were almost ineffective (group b) or much less effective (group c) in reducing gastric lesions.

Table I

Test 1 : Gastric tolerability of drugs representative of the drug classes illustrated in the present invention in animals not treated or treated with NEM (oxidative stress conditions). The % incidence is calculated from the ratio between the number of animals found with gastric lesions and that total of the group.

Compound	dose (mg/Kg) /admin. route	Gastro-enteropathy (% incidence)	
		without NEM	with NEM
carrier		0	0
Indomethacin	7.5/p.o.	0	100
Ambroxol	25/p.o.	0	80
Mesalamine	750/i.c.	0	60
Alendronate	15/p.o.	0	90
Tacrine	1/s.c.	0	100
Omeprazol	30/s.c.	0	0
Misoprostol	0.5/s.c.	0	0

p.o. = per os; i.c. = by intracolonic route;
s.c. = by subcutaneous route.

Table II

Test 2 : Inhibition of apoptosis (DNA fragmentation) induced by CIP in the endothelial cells in the presence of compounds representative of the drug classes illustrated in the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin	95
Paracetamol	120
Clopidogrel	110
Salbutamol	90
Ambroxol	70
Alendronate	160
Diphylline	95
Cetirizine	115
Enalapril	80
Nicotinamide	98
Ampicilline	94
Aciclovir	95
Mesalamine	74
Tacrine	90
Simvastatine	72
Omeprazol	90

Table III

Test 2 : comparison of the inhibition of apoptosis (DNA fragmentation), induced by CIP in endothelial cells in the presence of indomethacin and of a corresponding ester according to the present invention.	
Compound	Apoptosis % with respect to the controls treated only with CIP
Indomethacin (comp.)	95
Indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cisteine (ref. Ex. 3)	20

Table IV

Test 3 : Gastric tolerability (gastrointestinal damage incidence), hepatic (GPT dosage, glutamic-pyruvic transaminase), and cardiovascular (blood pressure) of some compounds representative of the drug classes illustrated in the present invention in conditions of endothelial trouble induced by L-NAME.
The results relating to the blood pressure and GPT are expressed as % values with respect to those found in the animals treated with the only carrier, without L-NAME.

Compound	dose mg/Kg /administ. route	Blood pressure %		GPT %		Gastroenteropathy %	
		without L-NAME	with L-NAME	without L-NAME	with L-NAME	without L-NAME	with L-NAME
Carrier		100	152	100	155	0	30
Paracetamol	300/i.p.	108	155	180	500	20	90
Doxorubicine	1/i.p.	120	145	195	360	30	100
Simvastatin	50/p.o.	85	148	122	220	0	60
Omeprazol	30/s.c.	100	150	100	160	0	10
Misoprostol	0.5/s.c.	100	142	100	160	0	5

Table V

Test 4: Screening of the effectiveness of the listed compounds in inhibiting radical production from DPPH.	
Compound	% inhibition radicals from DPPH
Solvent	0
N-acetylcisteine	100
Cisteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
Penicillamine	100

Table VI

Antiinflammatory activity (leucocyte infiltration with respect to the animals treated with carrier and pretreated with L-NAME), gastric tolerability and blood pressure (with respect to the animals not pretreated with L-NAME) of some drugs and of the corresponding compounds according to the present invention

Compound	dose mg/Kg	Leucocyte infiltration % inhibition	Blood pressure %	Gastropathy % incidence
Carrier	-	-	145	30
Diclofenac (comp.)	10	68	155	100
Diclofenac thioester with (4-nitroxy)butyryl penicillamine (Ex. 26)	10	70	115	20
Piroxicam (comp.)	10	78	145	100
Piroxicam ester with p-(4-nitroxy)butyryloxy ferulic acid (Ex. 25)	10	75	110	10
Acetylsalicylic acid (comp.)	50	60	160	100
Thioester acetylsalicylic acid with N-acetyl-(4-nitroxy) butyryl cisteine (Ex. 24)	50	55	110	0

Table VII

Test on gastric tolerability of the listed drugs and of the corresponding derivatives according to the present invention performed on rats not pretreated with L-NAME		
Compound	dose mg/Kg	Gastropathy % incidence
Carrier	-	-
Diclofenac	20/p.o.	70
Diclofenac derivative Ex. 26	20/p.o.	0
Ambroxol	100/p.o.	60
Ambroxol Derivative Ex. 9	100/p.o.	10
Alendronate	100/p.o.	90
Alendronic acid Derivative Ex. 10	100/p.o.	20
Tacrine	10/s.c.	80
Tacrine Derivative Ex. 17	10/s.c.	20

Table VIII

Test on gastric tolerability following oral administration of NEM (Ex. F8)		
groups	dose mg/Kg p.o.	Gastropathy % incidence
controls	-	-
group b - comparative mixture indomethacin (A) + N-acetylcysteine (B)	5(A)+2.3(B)	90
group c - comparative mixture indomethacin 4-(nitroxy)butyl ester (C) + N-acetylcysteine (B)	6.6(C)+ 2.3(B)	40
group d indomethacin thioester with N-acetyl-(4-nitroxy)butyryl cisteine	8.7	10

CLAIMS

1. Compounds or their salts having the following general formulas (I) and (II):

$$A—B—C\text{-}N(O)_s \qquad (I)$$

wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

A = $R—T_1$-, wherein

R is the drug radical and

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -$T_B—X_2—T_{BI}$- wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0, and tx = 0 when txx = 1; X is as above defined;

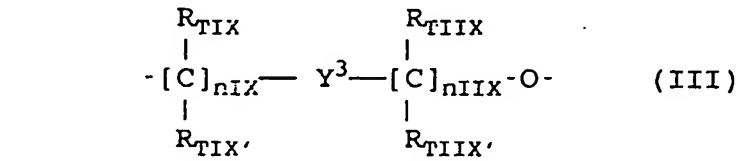
X_2 is a bivalent bridging bond as defined below;

C is the bivalent -T_C-Y- radical, wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is an alkylenoxy group R'O wherein R' is linear or

branched when possible C_1-C_{20}, preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring may have side chains of R' type, R' being as above defined; or



(III)

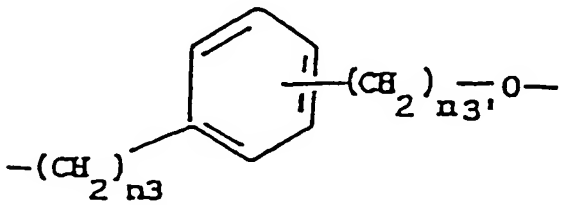
wherein:

nIX is an integer between 0 and 3, preferably 1;

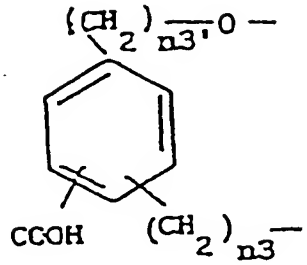
nIIX is an integer between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms.



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



wherein n3 and n3' have the above mentioned meaning

- $(CH_2\text{-}CH(ONO_2)\text{-}CH_2\text{-}O)_{nf'}$-

- -$(CH_2\text{-}CH(ONO_2)\text{-}CH_2\text{-}O)_{nf'}$-

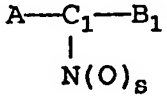
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- -$(CH(R_{1f})\text{-}CH_2\text{-}O)_{nf}$-

- -$(CH_2\text{-}CH(R_{1f})\text{-}O)_{nf}$-

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4;

preferably Y = -R'O- wherein R' is as above defined; preferably R' is a C_1-C_6 alkyl;

 (II)

wherein:

C_1 = $-T_{CI}-Y'(-T_{CII}-)$

wherein T_{CI} and T_{CII} are equal or different,

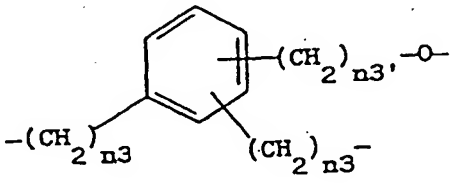
T_{CI}= (CO) when t = 0, T_{CI} = X when t' = 0, X being as above defined;

T_{CII}= $(CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that tI = 1 when tII = 0, and tI = 0 when tII = 1; X is as above defined;

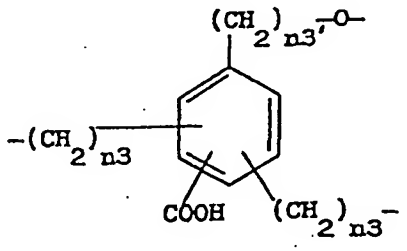
Y' is as Y above defined, but with three free valences instead of two, preferably:

- a $-R'(-O-$ group wherein R' is as above defined,

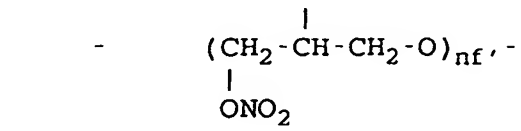
  preferably an alkyl from 1 to 6 carbon atoms, most preferably 2-4, or



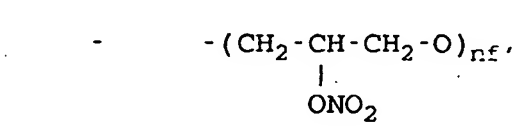
  wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



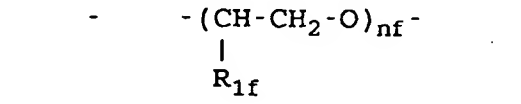
wherein n3 and n3' have the above mentioned meaning;



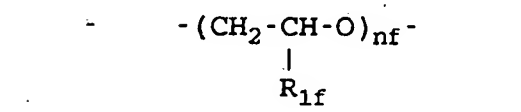
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



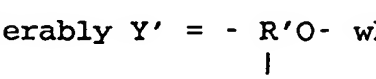
wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably Y' =  wherein R' is a linear or branched C_2-C_4, the oxygen which in Y' is covalently linked to the $-N(O)_s$ group is at the end of the free bond indicated in the formula of C_1;

B_1 = $-T_{BII}—X_{2a}$

wherein X_{2a} is a monovalent radical as defined below, T_{BII} = (CO) when tI = 0, T_{BII} = X when tII = 0, X being as above defined;

- X_2, bivalent radical is such that the corresponding precursor of B: $-T_B—X_2—T_{BI}-$ meets test 4, precursor in which the T_B and T_{BI} free valence are each saturated with -OZ, -Z, or with $-Z^I-\underset{|}{N}-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as defined below, depending on that T_B and/or T_{BI} = CO or X, in connection with the values of t, t', tx and txx;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}—X_{2a}$ meets test 4, precursor wherein the T_{BII} free valence is saturated with -OZ, -Z
or with $-Z^I-\underset{|}{N}-Z^{II}$, Z^I and Z^{II} being equal or or different and having the Z values as defined below, depending on that T_{BII} = CO or X, in connection with the tI and tII values;
- the drug A = $R—T_1-$, wherein the free valence is saturated as indicated hereinafter:
- when t' = O with:
  - O-Z wherein Z = H or R_{1a}, R_{1a} being a linear or branched when possible C_1-C_{10}

alkyl, preferably C_1-C_5, or with

- $-Z^I-N-Z^{II}$, Z^- and Z^{II} being as above defined,

- when t = 0 with -Z, wherein Z is as above defined,

with the proviso that the drug is not a steroid, is such to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula $A = R-T_1-$ wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier

+ NEM;

- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N-ω-nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such

as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrified, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I) and (II), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- the precursors of B or B_1 with the free valences saturated as above defined must meet test 4: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-di-phenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards the radical production by DPPH is calculated as a percentage by means of the following

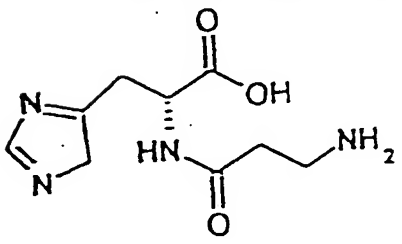
formula:

$$(1 - A_s/A_c)X100$$

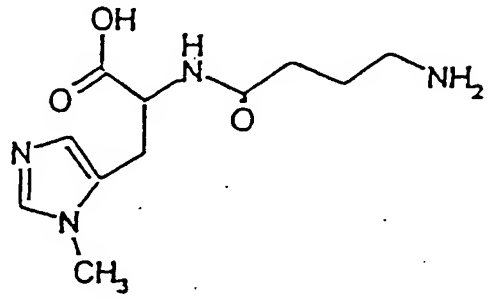
wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; the precursor complies with test 4 when the percentage of inhibition as above defined is equal to or higher than 50%.

2. Compounds according to claim 1 wherein the precursor compound of B or B. is selected from the following classes of compounds:

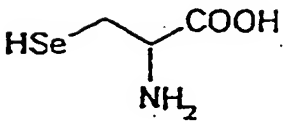
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetyl-penicillamine (CVI), cysteine (CVII), N-acetyl-cysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



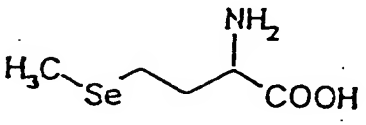
(CI)



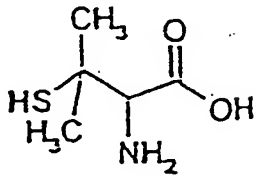
(CII)



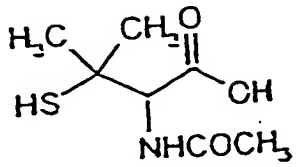
(CIII)



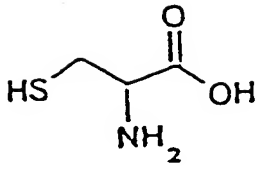
(CIV)



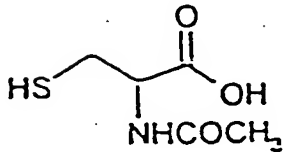
(CV)



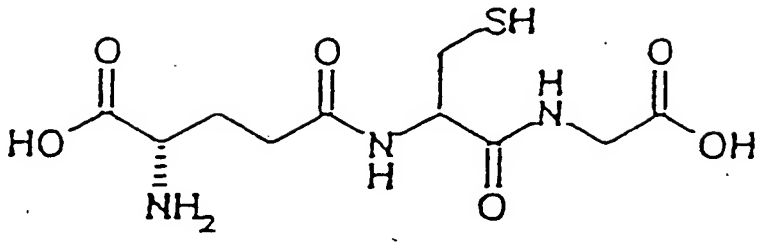
(CVI)



(CVII)

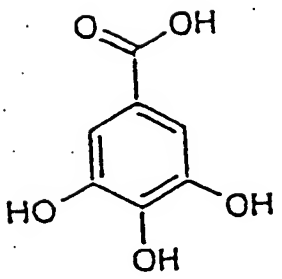


(CVIII)

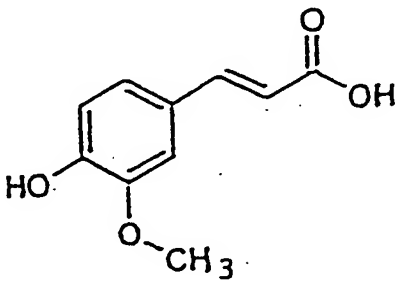


(CIX)

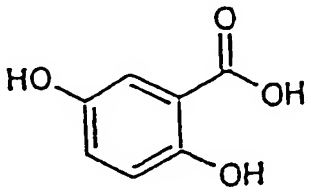
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



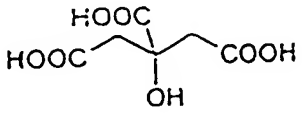
(DI)



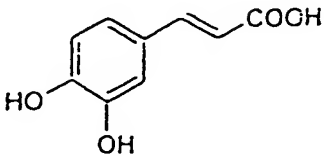
(DII)



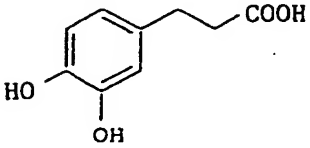
(DIII)



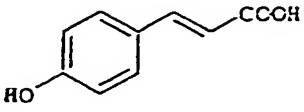
(DIV)



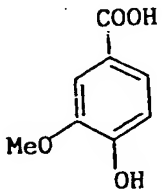
(DV)



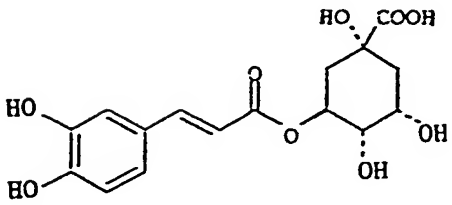
(DVI)



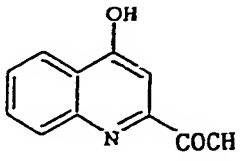
(DVII)



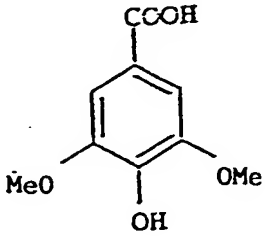
(DVIII)



(DIX)



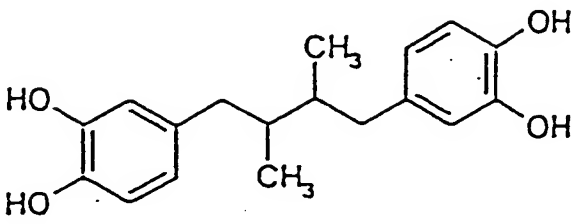
(DX)



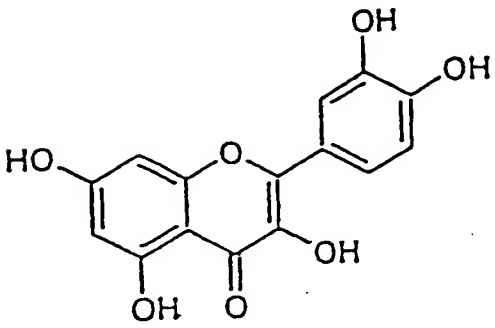
(DXI)

- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (E-

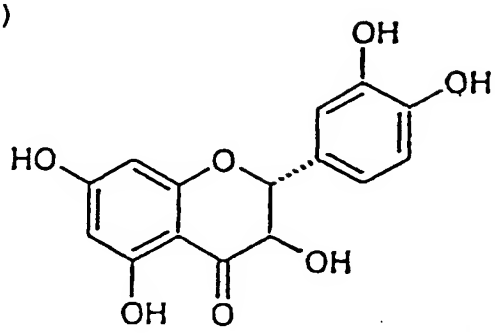
VI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxy-hydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-ter-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-ter-butyl-p-hydroxytoluene (EXX), p-ter-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thio-glycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EX-XVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



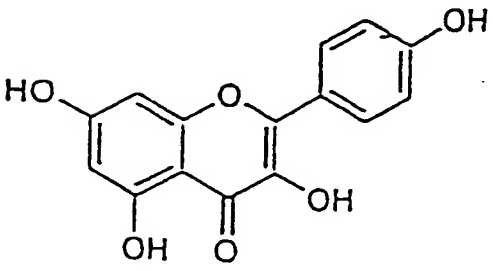
(EI)



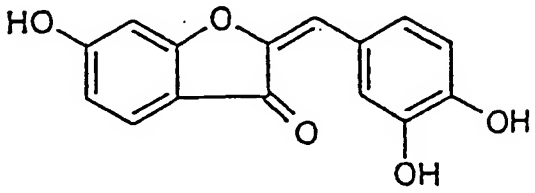
(EII)



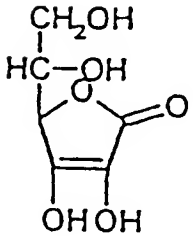
(EIII)



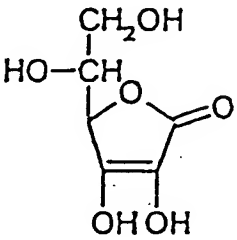
(EIV)



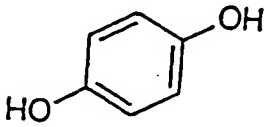
(EV)



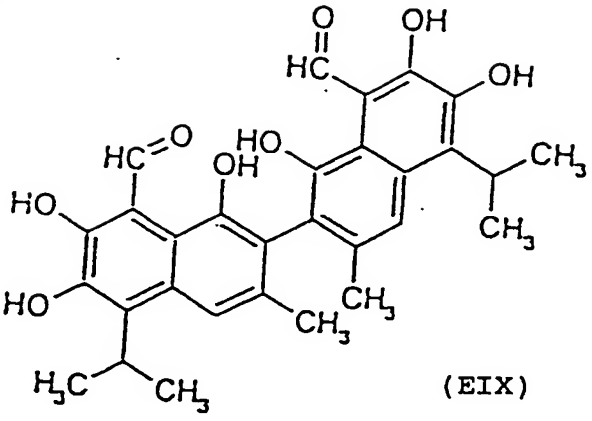
(EVI)



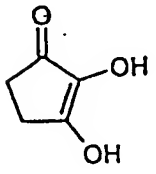
(EVII)



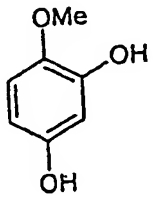
(EVIII)



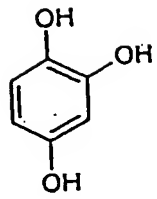
(EIX)



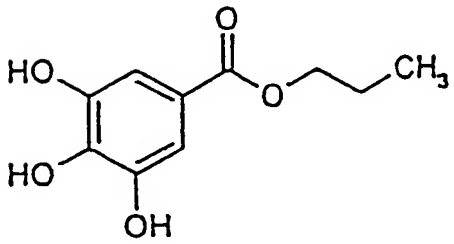
(EX)



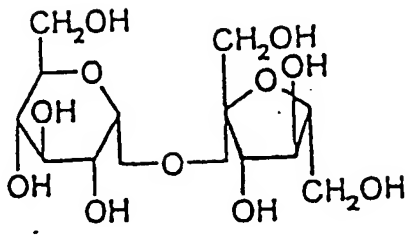
(EXI)



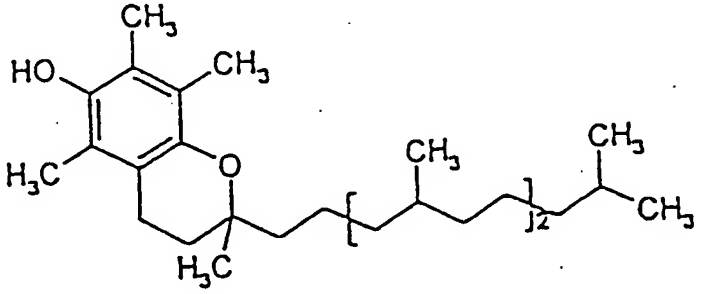
(EXII)



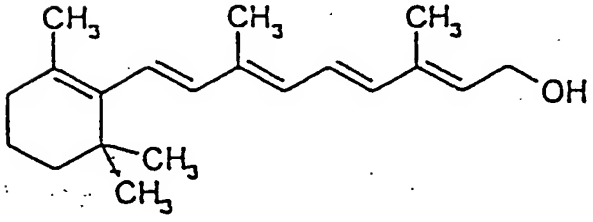
(EXIII)



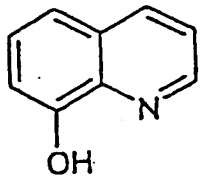
(EXIV)



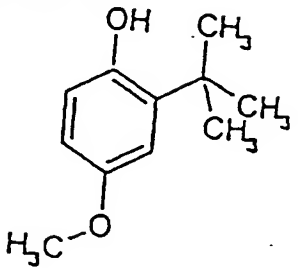
(EXV)



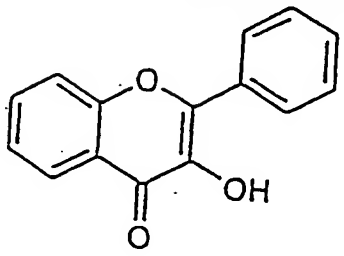
(EXVI)



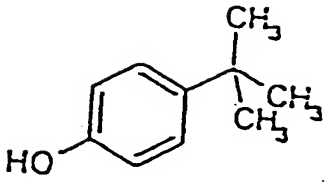
(EXVII)



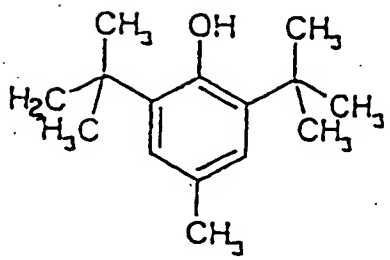
(EXVIII)



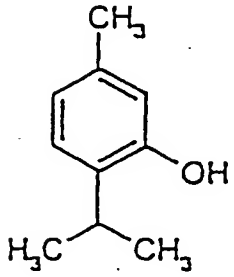
(EXIX)



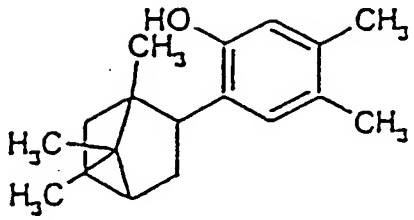
(EXXI)



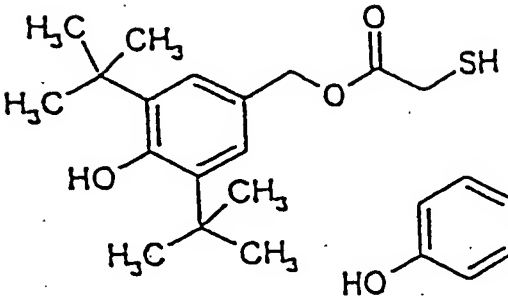
(EXX)



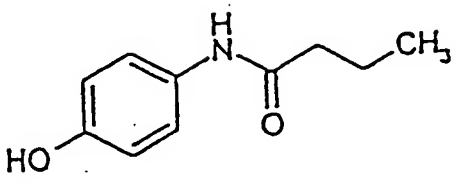
(EXXII)



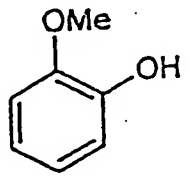
(EXXIII)



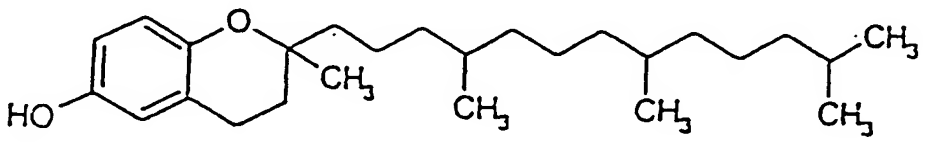
(EXXIV)



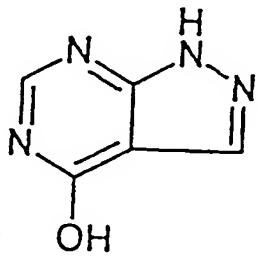
(EXXV)



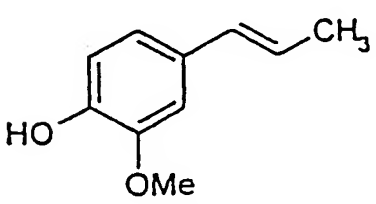
(EXXVI)



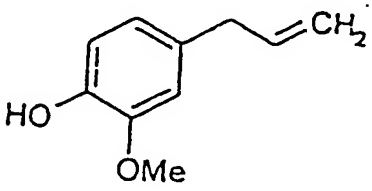
(EXXVII)



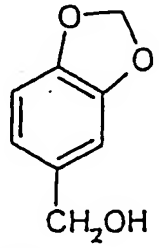
(EXXXI)



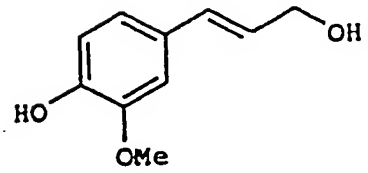
(EXXVIII)



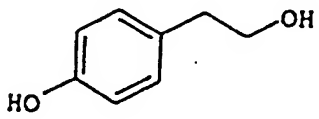
(EXXIX)



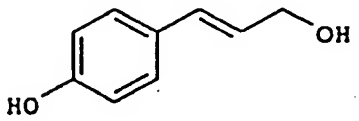
(EXXX)



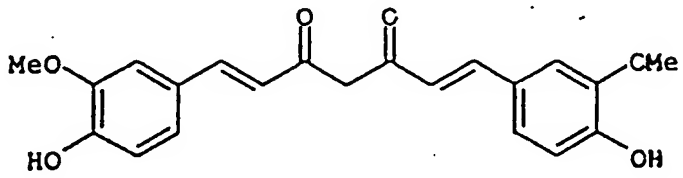
(EXXXII)



(EXXXIII)

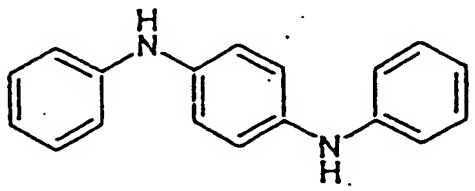


(EXXXIV)

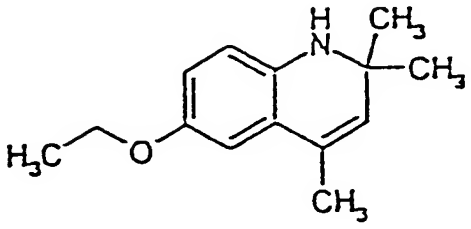


(EXXXV)

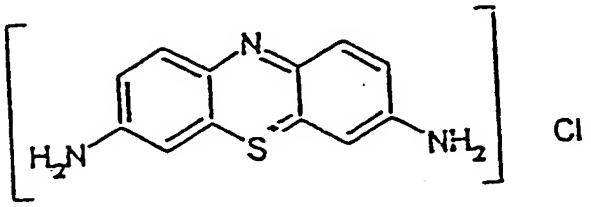
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



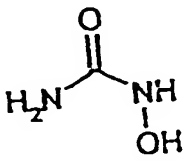
(MI)



(MII)

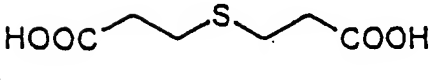


(MIII)

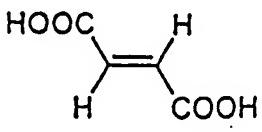


(MIV)

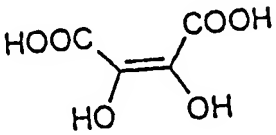
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thioctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylendioxycinnamic acid (NVII), piperonylic acid (NVIII):



(NI)

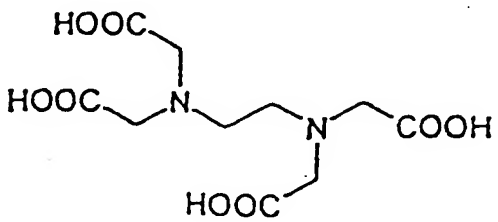


(NII)

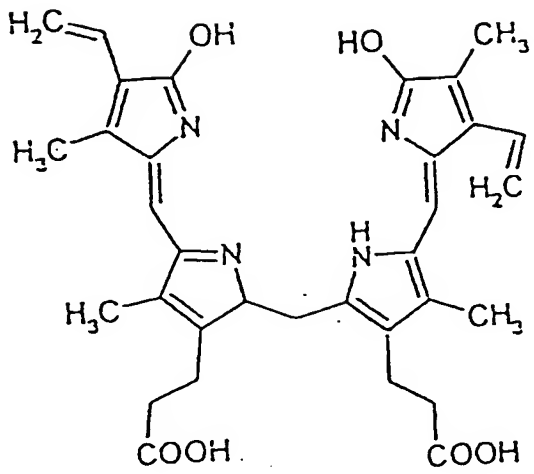


(NIII)

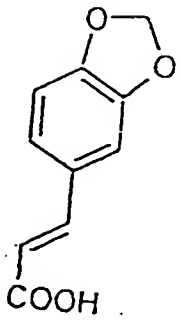
(NIV)



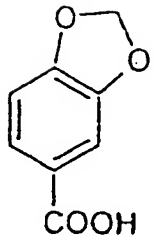
(NV)



(NVI)

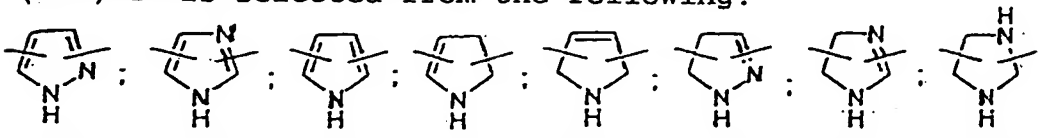


(NVII)

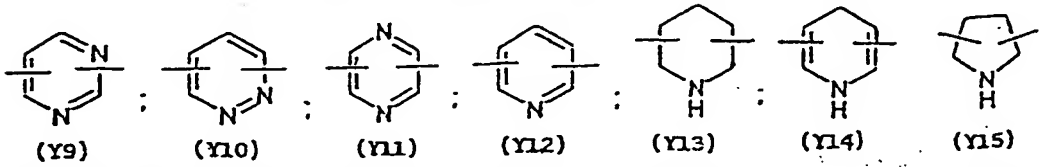


(NVIII)

3. Compounds according to claims 1-2, wherein in formula (III) Y^3 is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y7) (Y8)



(Y9) (Y10) (Y11) (Y12) (Y13) (Y14) (Y15)

4. Compounds according to claims 1-2, wherein Y' = -R'O- and Y = -R'O-, R' has 1-6 carbon atoms.

5. Compounds according to claims 1-4 wherein the precursor drugs of the compounds of formula (I) and (II) are selected from the following: anti-inflammatory, analgesic drugs, bronchodilators and drugs active on the cholinergic system, expectorant-mucolytic drugs, anti-asthmatic-antiallergic, antihistaminic drugs, ACE-inhibitors, beta-blockers, antithrombotic drugs, vasodilators, antidiabetic, antitumoral, antiulcer, antihyperlipidemic, antibiotic, antiviral drugs, bone reabsorption inhibitors, antidementia drugs.

6. Compounds according to claim 5, wherein the precursor drugs are selected from the following:
anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-aminoacetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, sodium diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-

acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol; analgesic drugs: acetaminophen, acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyrocetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, p-lactophenetide, levorphanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorphanol, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, phenocoll, phenoperidine, phenylbutazone, phenylsalicylate, phenylramidol, salicin, salicylamide, tiorphan, tramadol, diacerein, actarit; bronchodilators and drugs active on the cholinergic system: acefylline, albuterol, bambuterol, bamifylline, bevonium methyl sulphate, bitolterol, carbuterol, clenbuterol, chlorprenaline, dioxethedrine, difylline, ephedrine, epinephrine, eprozinol, etafredine, ethylnorepinephrine, etofylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetharine, isoprotenerol, mabuterol, metaproterenol, oxybutynin, oxitropium bromide, pirbuterol, procaterol, protokylol,

proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-teobromineacetic acid, tiotropium bromide, tretoquinol, tulobuterol, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-ylmethyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromhexine, domiodol, erdosteine, guaiacol, guaifenesin, iodinated glycerol, letosteine, mesna, sobrerol, stepronin, terpin, tiopronin;

antiasthmatic/antiallergic antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, histamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, urushiol, bromhexine;

ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naphthopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;

beta-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol,

sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;

antithrombotic and vasoactive drugs: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamole, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, heparin, lamifiban, midodrine, nadroparin, nicotinyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, triflusal, xanthinol niacinate;

antidiabetic drugs: acarbose, carbutamide, glibornuride glybuthiazol(e), miglitol, repaglinide, troglitazone, 1-butyl-3-metanyl-urea, tolrestat, nicotinamide;

antitumoral drugs: ancitabine, anthramycin, azacitidine, azaserine, 6-azauridine, bicalutamide, carubicin, carzinophilin, chlorambucil, chlorozotocin, cytarabine, daunorubicin, defosfamide, demecolcine, denopterin, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicin, droloxifene, edatrexate, eflornithine, enocitabine, epirubicin, epitiostanol, ethanidazole, etoposide, fenretinide, fludarabine, fluorouracil, gemcitabine, hexestrol, idarubicin, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, mycophenolic acid, ninopterin, nogalamycin,

paclitaxel, pentostatin, pirarubicin, piritrexim, plicamycin, podophyllic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, thiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicin;

antiulcer drugs: ε-acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazole, ornoprostil, pantoprazole, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;

anti-hyperlipidemic drugs: atorvastatin, cilastatin, dermostatin, fluvastatin, lovastatin, mevastatin, nystatin, pentostatin, pepstatin, privastatin sodium salt, simvastatin;

antibiotics: amdinocillin, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole,

ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracycline, cinoxacin, cyprofloxacin, clavulanic acid, clometocillin, cloxacillin, cyclacillin, cycloserine, demeclocycline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, meclocycline, meropenem, metampicillin, methacycline, methicillin sodium salt, mezlocillin, minocycline, moxalactam, mupirocin, myxin, negamycin, novobiocin, oxacillin, panipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, phenethicillin potassium salt, pipacycline, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidin, azithromycin, clarithromycin, dirithromycin, enviomycin, erythromycin, josamycin, midecamycin, miokamycin, oleandomycin, rifabutin, rifamide, rifamycin, rifaximin, rokitamycin, spiramycin, troleandromycin, viomycin, virginiamycin;

amikacin, apramycin, arbekacin, dibekacin, dihydrostreptomycin, fortimicins, gentamicin, micronomicin, neomycin, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomicin, tobramycin, trospectomycin;bacampicillin, cefcapene

pivoxil, cefpodoxime proxetil, panipenem, pivampicillin, pivcefalexin, sultamicillin, talampicillin;

carbomycin, clindamycin, lincomycin, mikamycin, rosaramicin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rufloxacin, sparfloxacin, tosufloxacin, trovafloxacin, clomocycline, guamecycline, oxytetracycline, nifurpirinol, nifurprazine;

p-aminosalicylic acid, p-aminosalicylic acid hydrazide, clofazimine, deoxydihydrostreptomycin, ethambutol, glyconiazide, isoniazid, opiniazide, phenyl aminosalicylate, rifampin, rifapentine, salinazid, 4-4'-sulfynyldianiline,

acediasulfone, dapsone, succisulfone, p-sulfanilylbenzyl amine, thiazolsulfone, acetyl sulfamethoxypyrazine, mafenide, 4'-(methylsulfamoyl)sulfanilanilide, salazosulfadimidine, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 2-p-sulfanilylanilinoethanol, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine,

sulfapyridine,sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfisomidine, sulfisoxazole, 4-sulfanilamido salicylic acid; negamycin, carumonan, cloxyquin, nitroxoline, arginine, metronidazole;

antiviral drugs: acyclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxin, ribavirin, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

bone reabsorption inhibitors: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;

antidementia drugs: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

7. Compounds according to claims 5-6, wherein the precursor drugs are selected from the following:

anti-inflammatory drugs: acetylsalicylic acid, 5-aminoacetylsalicylic acid, carprofen, diclofenac sodium salt, diflunisal, etodolac, flufenamic acid, flunixin, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, naproxen, niflumic acid, olsalazine, piroxicam, salsalate, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin, zomepirac, tomoxiprol;

analgesic drugs: acetaminophen, acetylsalicylsalicylic

acid, benoxaprofen, buprenorphine, butorphanol, capsaicin, diacereine, dihydrocodeine, ethylmorphine, eugenol, phenylbutazone, meptazinol, morphine, nalbuphine, pentazocine, thiorphan, tramadol, actarit;

bronchodilators drugs and drugs active on the cholinergic system: albuterol, carbuterol, clenbuterol, difylline, etofylline, fenoterol, ipratropium bromide, metaproterenol, oxybutynin, pirbuterol, salmeterol, terbutaline, tiotropium bromide, zaprinast, cyclodrine, NS-21, 2-hydroxy-2,2-diphenyl-N-(1,2,3,6-tetra hydro-pyridin-4-yl methyl)acetamide;

expectorant/mucolytic drugs: ambroxol, bromexine, guaiacol, sobrerol;

antiasthmatic/antiallergic antihistaminic drugs: cetirizine, chromoglycate, histamine, levocabastine, lodoxamide, montelukast, terfenadine, bromexine;

ACE-inhibitors: captopril, enalapril, lisinopril, losartan, ramipril;

beta blockers: alprenolol, atenolol, bupranolol, labetalol, metipranolol, metoprolol, pindolol, propranolol, timolol;

antithrombotic and vasoactive drugs: acetylsalicylic acid, acetorphan, argatroban, clopidogrel, dalteparin, dipyridamole, enoxaparin, heparin, iloprost, midodrine, ozagrel, phenylpropanolamine, trifusal;

antidiabetic drugs: tolrestat, nicotinamide;

antitumoral drugs: anthramycin, daunorubicin, doxorubicin, epirubicin, fluorouracyl, methotrexate, vinblastine;

antiulcer drugs: cimetidine, omeprazole, pantoprazole;

antihyperlipidemic drugs: lovastatin, pravastatin sodium salt, simvastatin;

antibiotics drugs: amoxicillin, ampicillin, aztreonam, biapenem, carbenecillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefoxitin, clavulanic acid, dicloxacillin, imipenem, meclocycline, methacycline, moxalactam, panipenem, sulbactam, azithromycin, erythromycin, josamycin, miokamycin, rifabutine, rifamide, rifamycin, gentamicin, paromomycin, sisomicin, bacampicillin, carbomycin, clindamycin, ciprofloxacin, clinafloxacin, difloxacin, enrofloxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pipemidic acid, apicycline, clomocycline, oxytetracycline, nifurpirinol, nifurprazine, isoniazid, rifampin, rifapentine, dapsone, thiazolsulfone, sulfamethoxazole, sulfamoxole, metronidazole, arginine;

antiviral drugs: aciclovir, famciclovir, ganciclovir, penciclovir, ribavirin, vidarabine, zidovudine;

bone resorption inhibitors: alendronic acid, etidronic acid, pamidronic acid.

8. Compounds or salts, or their compositions according to claims 1-7 for use as drugs.

9. Use of compounds or salts, or compositions thereof according to claims 1-7 for the preparation of drugs for the therapeutic stress-oxidative application.

10. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-7.